IJPSR (2012), Vol. 3, Issue 11 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 July, 2012; received in revised form 10 August, 2012; accepted 20 October, 2012

SYNTHESIS AND STUDY OF ANALGESIC, ANTI-INFLAMMATORY ACTIVITIES OF BIS (INDOLYL) METHANES (BIMs)

Partha Pratim Kaishap*, Chandrajit Dohutia and Dipak Chetia

Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh-786 004, Assam, India

Keywords:
Bis (indolyl) methane,
Indole,
Aldehyde,
Analgesic,
Anti-inflammatory

Correspondence to Author:

Partha Pratim Kaishap

Vill-Boalkamari, Po-Aminkata, Dist-Kokrajhar-783337, Assam, India

E-mail: pk6511@gmail.com

ABSTRACT

Gastro-intestinal (GI) toxicity is the common adverse effect which has been associated with most of NSAIDs available in the market. So the search for new therapeutic agents with high margin of safety and freedom from normally associated GI toxic effects has been a priority of pharmacologists and pharmaceutical industries. There are virtually limitless series of structurally novel heterocyclic compounds with a wide range of physical, chemical and biological properties. Literature survey reveals that coupling of two or more biodynamic molecules resulted in the enhanced biological activity. The present work embodied here involves synthesis and evaluation of analgesic and anti-inflammatory activities of some bis (indolyl) methane derivatives.

INTRODUCTION: Bis (indolyl) methanes, indole and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry and they exhibit various physiological properties. Indole ring system is the most important heterocycle available in natural compounds. Owing to great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural requirement in many pharmaceutical agents.

Indole has been widely identified as a privileged structure or pharmacophore, with its presence in over 3000 natural isolates [1] which are known to possess broad spectrum of biological activities and pharmaceutical applications [2]. Indomethacin [3] and tenidap [4] are indole derivatives found to possess anti-inflammatory activity with analgesic and anti-pyretic properties. They inhibit production of ecosanoids by inhibition of cyclo-oxygenase (COX) and thereby reduce edema. Several indole derivatives are reported to have anti microbial activity.

Bis (indolyl) methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism and induce apoptosis in human cancer cells [5]. Such compounds are prone to develop interesting bio activity and find useful applications as breast cancer preventive [6] and anti- bacterial agents [7].

Hong *et al.,* [8] and Kedmi *et al.,* [9] reported recently the potential beneficial effects of 3, 3-biindolyl methanes on the proliferation and induction of apoptosis in human prostate and breast cancer cells. Bis(Indolyl) methane derivatives have been reported to possess promising biological activities including antipyretic, antifungal, anti-inflammatory, anthelmintic, cardio-vascular, anticonvulsant, antimicrobial and selective COX-2 inhibitory activities [10].

QUICK RESPONSE CODE

IJPSR:
ICV (2011)- 5.07

Website:
www.ijpsr.com

Therefore synthesis of bis (indolyl) moiety has become interesting target for the synthetic organic chemist in view of their immense biological and pharmaceutical activities.

The survey of literature revealed that bis (indolyl) methane moiety has valuable biological activities and can be used for as an intermediate for synthesizing various heterocyclic moieties.

Compounds with electron releasing groups such as methoxy and hydroxyl group showed good anti-inflammatory and antimicrobial activity than those which do not have such groups. Compounds having pharmacophore such as chloro, fluoro, and bromo groups have exhibited best anti-convulsants [11], anti-inflammatory [12], anticancer [13], antitubercular [14], anti-bacterial activity [15], antifungal [16], and antihistaminic [17]. From the above discussions it may be concluded that the modifications in bis (indolyl) moiety displayed valuable biological activities and these modifications can be utilized to develop potentially active agents.

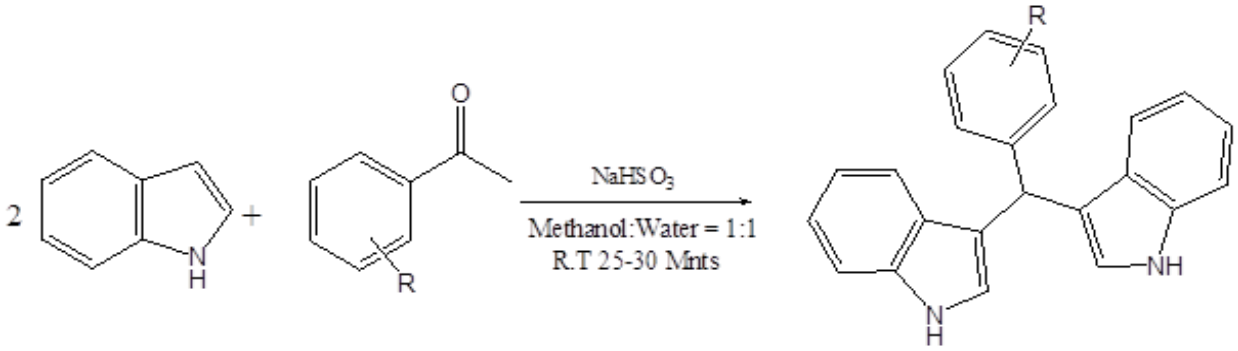
Most of the analgesic and anti-inflammatory drugs or NSAIDs available in the market are highly acidic in nature and having a common drawback of gastro intestinal toxicity [18]. So, there will be a search for new therapeutic agents with high margin of safety and which are free from generally associated G.I toxic effects such as ulceration, hemorrhage and perforation. In particular, bis (indolyl) methanes have received much attention in recent years [19].

In the light of these observations, few bis (indolyl) methane derivatives were synthesized with the objective of developing safer and potent analgesic and anti-inflammatory agents.

MATERIALS AND METHODS: All chemicals used were of laboratory grade and were procured from Merck specialities Pvt. Ltd. and Sisco Research Laboratories (SRL). Melting points were determined by Melting Point apparatus (*Veego, Model No. MP I*). The TLC plates were prepared by using Silica gel-G. The spots were visualized by exposure to iodine vapor and UV light.

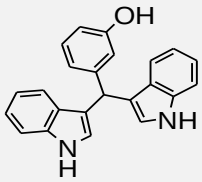
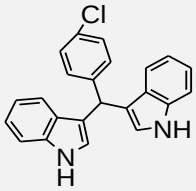
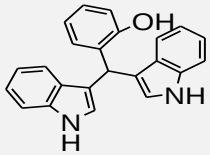
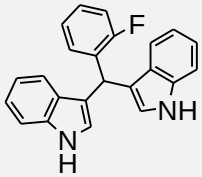
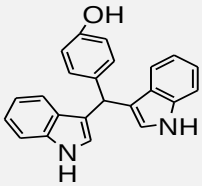
The UV-Spectra (λ_{max}) were recorded on *Shimadzu*, UV-1800, UV-VIS spectrophotometer. The FTIR spectra of the synthesized compounds were recorded on *Bruker FTIR* at the Lab. of Dept.of Pharm. Sciences, Dibrugarh University. The ^{1}H-NMR spectra were recorded in $CDCl_3$ 400.40 MHz by Bruker Advance-II 400 NMR spectrometer and the ^{13}C-NMR spectra were recorded in $CDCl_3$ at 100 MHz by Bruker Advance–II 100 NMR spectrometer. The mass spectra of the synthesized compounds were recorded on ZQMAA-255 equipped with an Electrospray Ionizer as an ionization method at SAIF-NEHU, Shillong. The *in vivo* experiments were performed after the approval of the protocol by the Institutional Animal Ethics Committee – MC/UCMS/IAEC/DU/04.

Synthesis of Bis (Indolyl) Methane Derivatives: To a mixture of indole 0.293g (2.5 mmole), substituted aldehydes 1.25 mmole in methanol: water (1:1), sodium bisulfite 20 mmole % (1.89g in100ml water) were added and stirred at room temperature for half an hour. When the reaction was complete, it was extracted trice with dichloromethane (10 ml), the combined organic layer was dried using anhydrous sodium sulphate, filtered and solvent was evaporated. The crude products were purified by column chromatography over silica gel (ethyl acetate: petroleum ether, 4:6 v/v). A total number of five Bis (Indolyl) Methane derivatives were synthesized and summarized in the **table 1**.



Indole Substituted Aldehyde Bis (Indolyl) Methane

TABLE 1: REACTION DETAILS OF THE SYNTHESIZED COMPOUNDS

Compound Code	Substitution (R)	Compound Name	Compound Structure	Molecular Weight	Yield (%)
BIM 1	m- Hydroxy	Bis(indolyl)-3-hydroxy phenyl methane		338.40	72
BIM 2	p- Chloro	Bis(indolyl)-4-chloro-phenyl methane		356.85	63
BIM 3	o- Hydroxy	Bis(indolyl)-2-hydroxy-phenyl methane		338.40	68
BIM 4	o- Fluoro	Bis(indolyl)-2-fluoro-phenyl methane		340.39	73
BIM 5	p- Hydroxy	Bis (indolyl)-4-hydroxy- phenyl methane		338.40	70

Evaluation of Biological activities:

1. **Animals:** Male Swiss albino mice (25-40 g) and male Wistar rats (120-160 g) were used to carry out the analgesic and anti-inflammatory studies of the synthesized Bis (Indolyl) Methane derivatives respectively. Animals were acclimatized in the animal house for at least one week prior to experimentation. Animals were kept at 22 ± 3^0 C and 55 ± 5% relative humidity during the whole experiment. Standard food pellets and water were supplied *ad libitum*. The experiments were performed after the approval of the protocol (Approval No-MC/UCMS/IAEC/DU/04) by the Institutional Animal Ethics Committee (Rgtn. No-1576/ GO/ a/11/ CPCSEA dtd. 17.02.2012).

2. **Acute Toxicity Studies:** Toxicological studies of the test compounds as a suspension in 1% Tween 80 were carried out by administering high dose of 1000mg/kg and low dose 100mg/kg body weight in Swiss albino mice. The control group received 1% Tween 80 suspension. Animals were kept in fasting condition prior to dosing. Following the period of fasting, the animals were weighed, properly marked and the test substance administered. After administration of test compounds, food was withheld for a further 1-2 hours. OECD guideline No. 420; (Annexure -2d) method of CPCSEA was adopted for toxicity studies.

Animals were observed individually after dosing at least once during the first 30 minutes, periodically during the first 24 hours, with special attention given during the first 4 hours and daily thereafter, for a total of 14 days. After carrying out the acute toxicity study of all the test compounds, it was found that the entire compounds in the present investigation were non-toxic up to 1000mg/kg body weight.

3. **Analgesic Activity:** Analgesic activity of the synthesized compounds was carried out using the Acetic acid writhing method in Swiss Albino mice by *Seigmund et al* [20]. 19 groups of mice, male and female weighing 25-40g were taken with 5 in each group. Acetic acid (0.6 %) was used as an irritant and administered intraperitonally for the control group and the number of writhing movements were noted and recorded for a time span of 15 minutes. The test compounds and the standard drug (Aspirin) were given in doses of 100mg, 250 mg and 500 mg per kg body weight orally half an hour prior to the administration 1ml (0.6 %) acetic acid injection. The number of writhings which the animal demonstrated within a span of 15 minutes were noted and reported.

4. **Anti-inflammatory Activity:** For Anti-inflammatory studies the method described by Winter *et al* [21] was followed. Acute inflammation was produced by injecting 0.1ml of carrageenan 1% suspension in 1% Tween 80 under the planter aponeurosis of the left hind paw of Wistar rats. 7 groups of rats were used each group containing 5 animals. The control group received vehicle (1%Tween 80). The standard drug Diclofenac and the test compounds were administered orally one hour prior to the carrageenan injection. Hind paw volume was recorded for each group after intervals of ½, 1, 2 and 3 hours. Initial as well as the oedema volume was measured by Plethysmograph.

RESULTS AND DISCUSSION: A new series bis (indolyl) methane derivative have been synthesized and screened for their analgesic and anti-inflammatory activities. Various physico-chemical data of the synthesized compounds obtained are recorded in the **table 2**.

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF THE SYNTHESIZED COMPOUNDS

COMPOUND CODE	STATE	COLOUR	M. POINT (0^0C)	SOLUBILITY	R_f(TLC)*
BIM-1	Solid	White	104-105	Methanol, ethanol, acetone	0.75
BIM-2	Solid	Pale yellow	78-80	Methanol, ethanol, acetone	0.47
BIM-3	Solid	Reddish white	118-120	Methanol, ethanol, acetone	0.81
BIM-4	Solid	White	76-79	Methanol, ethanol, acetone	0.52
BIM-5	Solid	Light orange	124-126	Methanol, ethanol, acetone	0.73

*Solvent system of TLC-hexane: ethyl acetate :: 9:1 for all the compounds.

The UV λ_{max} (nm) values of synthesized compounds are given in **Table 3** along with characteristic FTIR absorption bands of different functional groups and m/z values of the intense peaks with abundance. The ^{1}H- and ^{13}C-NMR spectral data are also assigned in the **table 3**.

TABLE 3: SPECTRAL PARAMETERS OF THE SYNTHESIZED COMPOUNDS

COMPD. CODE	FTIR SPECTRUM	UV λ_{max} (nm) Ethanol	MS (*m/z*%)	^{1}H- NMR -and ^{13} C-NMR spectra
BIM-1	930.09(C-C stretch), 1055.21(C-O stretch), 1243.48 (C-N Aromatic ring), 1452.02(C=C, Aromatic ring), 3042.74 (C-H stretch), 3391.99 (N-H stretch), 3624.22 (O-H stretch).	279.5	339.28	**^{1}H NMR (400 MHz, $CDCl_3$):** δ, ppm: 5.043(s, H, OH), 5.491(s, H, CH methine), 6.524-7.853 (m, 10H, CH 2 indole ring), 9.198 (s, H, NH). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ, ppm: 76.853-77.489, 102.580, 111.179, 119.904-124.314, 127.903, 135.830.
BIM-2	742.14(C-Cl stretch), 929.75(C-C stretch), 1242.28 (C-N Aromatic ring), 1451.22(C=C, Aromatic ring), 3040.28 (C-H stretch), 3392.921 (N-H stretch).	286.5	355.14	**^{1}H NMR (400 MHz, $CDCl_3$):** δ, ppm: 6.020 (s, H, CH methin), 6.557 (m, 4H CH phenyl ring), 7.174-7.929(m, 10H, CH 2 indole ring), 9.125 (s, H, NH). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ, ppm: 39.783, 77.073-77.711, 102.540, 111.449, 119.107-130.318, 135.928, 136.808.
BIM-3	930.10(C-Cstretch), 1055.14(C-O stretch), 1243.68 (C-N Aromatic ring), 1453.13(C=C, Aromatic ring), 3038.49 (C-H stretch), 3391.43 (N-H stretch), 3626.24 (O-H stretch).	279.0	337.07	**^{1}H NMR (400 MHz, $CDCl_3$):** δ, ppm: 5.036(s, H, OH), 6.481 (s, H, CH methin), 6.949-7.211 (m, 4H CH phenyl ring), 7.613-7.824(m, 10H, CH 2 indole ring), 9.685 (s, H, NH). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ,ppm: 77.013-77.650,102.463, 111.374, 119.939, 120.873, 122.066, 124.557, 127.966, 135.917.

BIM-4	929.30(C-C stretch), 1241.21 (C-N Aromatic ring), 1330.03 (C-F stretch), 1449.76(C=C, Aromatic ring), 3041.53 (C-H stretch), 3397.82 (N-H stretch).	298.5	339.30	**^{1}H NMR (400 MHz, $CDCl_3$):** δ, ppm: 5.936 (s, H, CH methin), 6.187-6.887 (m, 4H CH phenyl ring), 6.906-7.521 (m, 10H, CH 2 indole ring), 9.012 (s, H, NH). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ, ppm: 32.580, 76.905-77.540, 102.551, 111.249, 115.266-131.057,
BIM-5	930.42 (C-Cstretch), 1035.66 (C-O stretch), 1242.82 (C-N Aromatic ring), 1452.87(C=C, Aromatic ring), 3040.62 (C-H stretch), 3393.68 (N-H stretch), 3625.98 (O-H stretch).	280.0	337.18	**^{1}H NMR (400 MHz, $CDCl_3$):** δ, ppm: 5.775 (s, H, OH), 6.507 (s, H, CH methin), 6.507-6.782 (m, 4H CH phenyl ring), 6.970-7.731(m, 10H, CH 2 indole ring), 9.781 (s, H, NH). **^{13}C-NMR (100 MHz, $CDCl_3$):** δ, ppm: 76.860-77.475, 102.564, 111.179, 119.267-124.325, 127.095-136.750.

Analgesic Activity: Synthesized compounds were evaluated for analgesic activity by acetic acid induced writhing method. The percentages of analgesic activity of the synthesized compounds at three different doses calculated are listed in the **Table 4**.

TABLE 4: ANALGESIC ACTIVITY OF BIS (INDOLYL) METHANES

Group	No. of writhings noted for 15 minutes			Percentage of analgesic activity		
	100 mg/ kg Dose	250 mg/ kg Dose	500 mg/ kg Dose	100 mg/ kg Dose	250 mg/ kg Dose	500 mg/ kg Dose
Control		103.67±1.02			-	
Aspirin	52±1.24**	41±3.26**	32±0.36**	49.84	60.45	69.13
BIM 1	61±2.44**	43±1.63**	39.65±1.69**	41.16	58.52	61.73
BIM 2	78.87±0.47*	68±3.26*	50.33±2.05*	24.11	34.41	51.45
BIM 3	75±0.81*	70±0.82*	62.30±1.24*	27.65	32.48	39.88
BIM 4	70±0.82**	61±0.72**	46.35±1.25**	32.48	41.16	55.31
BIM 5	73.8±2.92*	66±3.16*	50.25±3.69*	28.81	36.34	51.53

No. of writhings are expressed in mean ± SE (n=5). Statistical analysis is carried out by using one way ANOVA (F-test) followed by Dunnett's t test. **Significantly different from the control value at P<0.001 and *Significantly different from control value at P<0.01.

Anti-inflammatory Activity: Anti-inflammatory activity of the synthesized compounds were determined by carrageenan induced rat paw edema method and listed in **table 5 and figures 1 & 2** .

TABLE 5: ANTI-INFLAMMATORY ACTIVITY OF BIS (INDOLYL) METHANES

Group	Increase in paw volume (ml)				% of anti-inflammatory activity			
	½ Hour	1 Hour	2 hour	3 hour	½ Hour	1 Hour	2 hour	3 hour
Control	0.25±0.02	0.35±0.03	0.55±0.02	0.77±0.01			-	
Diclofenac	0.12±0.01**	0.17±0.06**	0.22±0.03**	0.26±0.07**	42	48.48	60	66.23
BIM 1	0.18±0.03*	0.21±0.02*	0.25±0.02*	0.28±0.07*	28	36.36	54.54	63.63
BIM 2	0.21±0.03*	0.25±0.07*	0.27±0.01*	0.31±0.06*	16	24.24	50.90	59.74
BIM 3	0.15±0.08**	0.21±0.01**	0.23±0.03**	0.27±0.02**	40	46.36	58.18	64.93
BIM 4	0.18±0.02*	0.25±0.01*	0.27±0.01*	0.28±0.02*	28	34.14	50.90	63.63
BIM 5	0.19±0.01*	0.22±0.02*	0.28±0.01*	0.33±0.06*	24	33.33	49.10	57.14

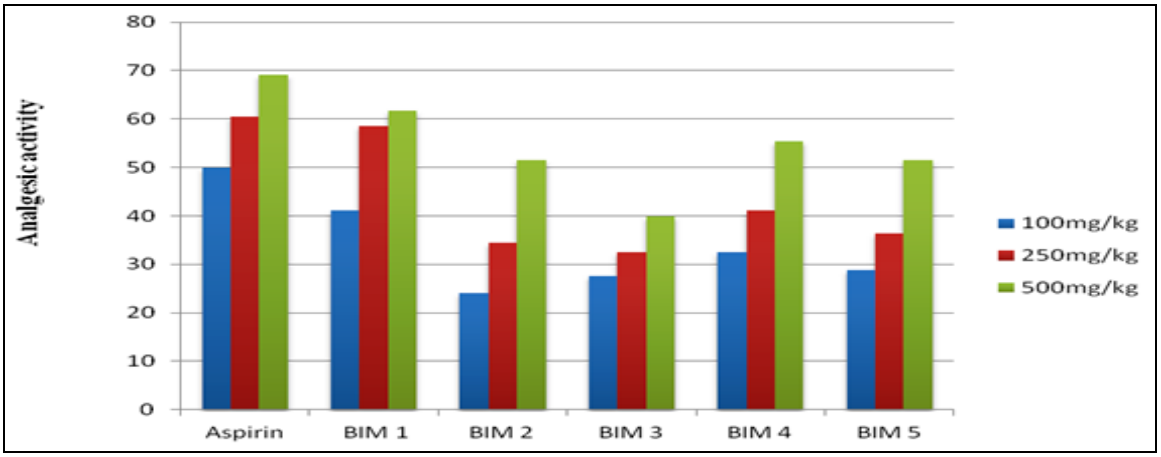


FIG. 1: HISTOGRAM OF SYNTHESIZED COMPOUNDS SHOWING ANALGESIC ACTIVITY

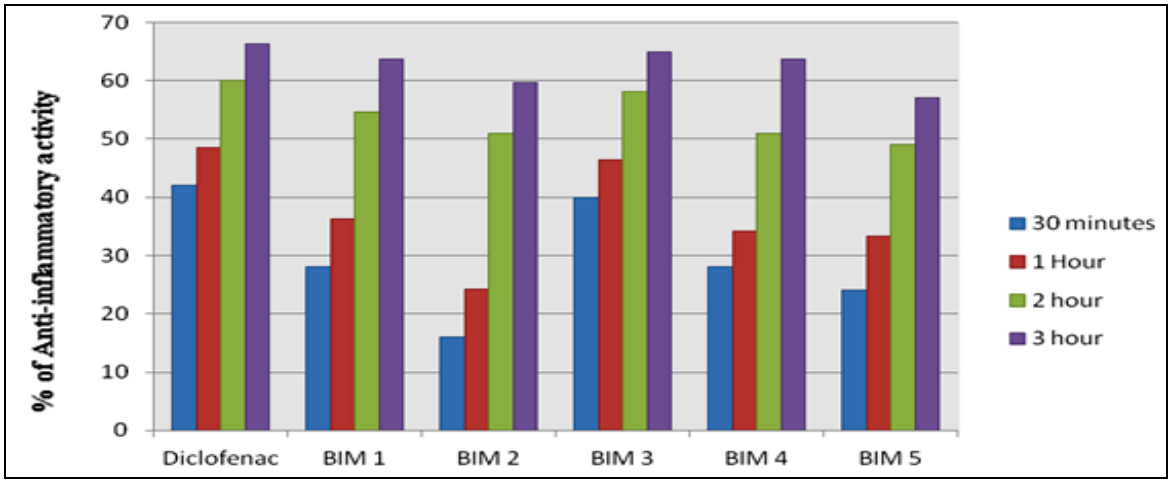


FIG. 2: HISTOGRAM OF SYNTHESIZED COMPOUNDS SHOWING ANTI-INFLAMMATORY ACTIVITY

CONCLUSION: Synthesis and study of acute toxicity, analgesic and anti-inflammatory activity of bis (indolyl) methanes in mice and rats have been carried out and described here. In acute toxicity study, no mortality was observed in the test compounds. The compounds were found safe in between the dose of 100 mg/kg to 1000mg/kg. However, further detailed toxicological investigations are required particularly to elucidate their chronic toxicity.

The results obtained clearly indicate that the synthesized compounds possess significant analgesic as well as anti-inflammatory activity at a dose of 500 mg/kg. Among the five synthesized compounds, the compounds BIM 1 (61.73%), BIM 2 (51.45%), BIM 4 (55.31%) and BIM 5 (51.53%) showed significant analgesic activity as compared to the standard Aspirin, whereas compound BIM 3(39.88%) have shown moderate activity.

The compound **BIM 1** is found to possess most effective analgesic activity among the all synthesized compounds. In case of anti-inflammatory study, all the compounds have shown significant activity as compared to the standard drug Diclofenac. The compounds **BIM 1** (63.63%), **BIM 3** (64.93%) and **BIM 4** (63.63%) have shown most effective anti-inflammatory activities.

Hence, it is concluded that **BIM-1** and **BIM 4** might be attractive candidates for further development as they are the most active compounds among the compounds that have both analgesic and anti-inflammatory activities.

The experimental details of the scheme of synthesis of the compounds reported here have been carefully documented, so that it may pave the way for researchers in their effort to make new analgesic and anti-inflammatory compounds in future.

ACKNOWLEDGEMENT: Authors are grateful to the Department of Pharmaceutical Sciences, Dibrugarh University for providing laboratory facilities, and the faculty members of Department of Pharmacology and Toxicology, College of Veterinary Science, Guwahati for providing technical support on animal studies. Kaishap and Dohutia acknowledge the All India Council for Technical Education, New Delhi for providing GPAT scholarship during the study.

REFERENCES:

1. Bell R, Carmeli S & Sar N: Vibrindole A, a metabolite of the marine bacterium, Vibrio parahaemolyticus, isolated from the toxic mucus of the boxfish Ostracion cubicus. *J Nat Prod*, 1994; 57: 1587.
2. Sundburg RJ: *The chemistry of Indoles*. Academic Press, New York 1996.
3. Kumar A, Sharma A, Nidhi M, Preethi S, Kabita K *et al*: Synthesis of Anti-inflammatory, analgesic and COX-II inhibitory activities of indolylpyrazolines. *Indian J Chem,* 2004; 43(B): 1532.
4. Moore PF, Larson DL, Otterness IG, Weissman A, Kadin SB *et al*: Tenidap, a structurally novel drug for the treatment of arthritis: antiinflammatory and analgesic properties. *J Carty Inflamm Res,* 1996; 45(2): 54.
5. Zeligs MA: Diet and estrogen status: the cruciferous connection, J Medicinal Foods J Med Food 1998; 1: 67.
6. Michnovicz JJ & Bradlow HL: A new approach to the prevention of breast cancer. *Proc R Soc Edinburg,* 1989; 95B: 1571.
7. Osawa T & Namiki M: Structure elucidation of streptindole, a novel genotoxic metabolite isolated from intestinal bacteria. *Tetrahedron Lett*, 1983; 24: 4719.
8. Hong C, Firestone GL & Bjeldanes LF: Cytostatic effects of 3, 3'-diindolylmethane in human endometrial cancer cells result from

an estrogen receptor-mediated increase in transforming growth factor-alpha expression. *Biochem Pharmacol,* 2002; 63: 1085

9. Nachshon-Kedmi MN, Yannai S, Haj A & Fares FA: Indole-3-carbinol and 3,3'-diindolylmethane induce apoptosis in human prostate cancer cells**.** *Food Chem Toxicol,* 2003; 41: 745.
10. Sujatha K, Perumal. PT, Muralidharan. D and Rajendran M: Synthesis, analgesic and anti-inflammatory activities of Bis (indolyl) methanes..*Indian journal of chemistry*, 2009; 48(B): 267-272.
11. Falco JL, Pique M., Gonzalez M., Buira.I, Mendez E et al: Synthesis, pharmacology and molecular modeling of *N*-substituted 2-phenyl-indoles and benzimidazoles as potent $GABA_A$ agonists. *Europian Journal of Medicinal Chemistry* 2006; 41: 985-990.
12. Rani P, Srivastava VK, Kumar A: Synthesis and antiinflammatory activity of heterocyclic indole derivatives. *Europian Journal of Medicinal Chemistry* 2004; 39: 449-452.
13. Lee EJ, Lee HJ, Park HJ, Min HY, Suh ME et al: Induction of G2/M cell cycle arrest and apoptosis by a benz[f]indole-4, 9-dione analog in cultured human lung (A549) cancer cells. *Bioorganic & Medicinal Chemistry Letter* 2004; 14: 5175-5178.
14. Karthikeyan SV, Perumal S, Shetty KA, Yogeeswari P and Sriram D: A microwave-assisted facile regioselective Fischer indole synthesis and antitubercular evaluation of novel 2-aryl-3,4-dihydro-2*H*-thieno[3,2-*b*]indoles. *Bioorganic & Medicinal Chemistry Letter* 2009; 19: 3006-3009.
15. Leboho TC, Tlabo C, Michael JP, Otterlo WA, Vuuren SF and Koning CB: The synthesis of 2- and 3-aryl indoles and 1, 3, 4, 5-tetrahydropyrano [4,3-*b*] indoles and their antibacterial and antifungal activity. *Bioorganic & Medicinal ChemistryLetters,* 2009; 19: 4948-4951.
16. Tiwari RK, Verma AK, Chhillar AK, Singh DJ, Sankar VK et al: Synthesis and antifungal activity of substituted-10-methyl-1,2,3,4-tetrahydropyrazino[1,2-a]indoles. *Bioorganic & Medicinal Chemistry* 2006; 14: 2747-2752.
17. Derek C, Cole DC, Ellingboe JW, Lennox WL, Mazandarani H et al: N_1-arylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivatives are potent and selective 5-HT_6 receptor antagonists. *Bioorganic & Medicinal Chemistry Letter* 2005; 15: 379–383.
18. Kant G, Parate A & Chaturbedi SC: QSAR Study Of Substituted 3, 5-Di-Tert-Butyl-4-Hydroxy Styrene : A Series With Antiinflammatory Activity. Indian Journal of Pharm Sci, 2005; 67: 116.
19. Garbe TR, Kobayashi M, Shimuju N, Takesue N, Ozawa M & Yukawa H: Indolyl carboxylic acids by condensation of indoles with alpha-keto acids. *J Nat Prod,* 2000; 63(5): 596.
20. Seigmund E, Cadmus R & Lu G: A method for evaluating both non-narcotic and narcotic analgesics. *Proc Soc Exp Biol Med* 1957; *95*: 729-731.
21. Winter C A, Riseley EA, Nuss G W, 1962. Carrageenan-induced edema in the hind paw of the rat as an assay for anti-inflammatory drugs. Proceeding of the Society of Experimental Biology Medicine, 1962; 111: 544–547.

How to cite this article:
Kaishap PP, Dohutia C and Chetia D: Synthesis and Study of Analgesic, Anti-Inflammatory Activities of bis iIndolyl) methanes (BIMs). *Int J Pharm Sci Res*. 3(11); 4247-4253.