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Research Article

SYNTHESIS AND CHEMICAL CHARACTERIZATION OF BENZIMIDAZOLE FUSED BENZOPYRAN DERIVATIVES AND EVALUATION OF THEIR ANTI-BACTERIAL POTENCY

Rufaida Farheen *, Y. Rajesh Babu [1]

** Department of Pharmaceutical Chemistry, Sultan-Ul-Uloom College of Pharmacy, Banjara Hills, Hyderbad-500 038, T.S, INDIA.*

[1] Professor and HOD Department of Pharmaceutical Chemistry, Sultan-Ul-Uloom College of Pharmacy, Banjara Hills, Hyderbad-500 038, T.S, INDIA.

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ABSTRACT

Benz-imidazole fused benzopyran derivatives were prepared by the reaction of 2-(1H-Benzo[d]Imidazol-2-yl)-1phenyl-1H-Benzo[f]chromeno-3-amine with different substituted benzaldehydes. The resulting derivatives were subjected to physical and chemical characterization. The anti-bacterial potency of the synthesized compounds was tested against a set of Gram positive and negative bacteria. The compound 9-(2-methoxyphenyl)-16-phenyl-16H-benzo[4,5]imidazo[1,2-c]benzo[5,6]chromeno[3,2-e]pyrimidine exhibited most potent activity. Detailed toxicological studies and molecular modelling would be beneficial in developing new drugs.

KEYWORDS: *Benzimidazole, Benzopyran, Coumarin, Anti-Bacterial, Disc-Diffusion.*

INTRODUCTION

Benzopyrans have been known as chromans, chromanones, chromones and 2-and 3-chromenes; coumarins being the largest class of benzopyran derivatives. The prenyl group found in coumarins are responsible for the biogenetic modifications such as cyclisation to dihydropyran, pyran, dihydrofuran, furans. In the Compound Index coumarins are subdivided as furo-1-benzopyran and pyrano-1-benzopyrans based on their oxygen substitution patterns [1-3].

Naturally occurring flavonoids contains 4H-1-benzopyran-4-one ring system and exhibits numerous biological activities-antiviral, anti-inflammatory, anti-allergic, anti-mutagenic and anticarcinogenic activities [4-6]. Coumarins or benzo-2-pyrone is the sweet smelling constituent found in white clover. Coumarin nucleus is widely found in nature and forms an important class of oxygen heterocycles. Extensive research for the development of synthetic analogues is due to the varied medicinal properties associated with coumarins [7-10].

The potency of molecule is increased when one biologically active molecule is linked to another. Thus, we plan to fuse Benz-imidazole and benzopyran moieties and the combination is anticipated to result in substantial increase in anti-bacterial activity.

***Corresponding author:**
Rufaida Farheen
Department of Pharmaceutical Chemistry,
Sultan-Ul-Uloom College of Pharmacy, Banjara Hills,
Hyderbad-500 038, T.S, INDIA.
** E-mail: farheenrufaida@gmail.com*

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MATERIALS AND METHOD

Melting points were determined by using Toshniwal apparatus in open capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel G plates using n-hexane : ethylacetate (1:3) solvent system and UV lamp used as visualizing agent. ^{1}HNMR spectra on a Varian EM-200, advance 200 mHz spectrophotometry using DMSO as solvent and TMS as internal standard (chemical shift values expressed in ppm).

Preparation of 2-(1H-BENZO[d]imidazol-2-yl)acetonitrile (I):

A mixture of benzene-1,2-diamine (10.8 gm, 0.1 mol) and ethyl 2-cyanoacetate (17 gm, 0.15 mol) were placed in a round bottom flask fitted with a condenser and refluxed for 1 hour. The liquid was vaporized to small quantity and cooled. The separated solid was then filtered, washed with ether and dried. The product was recrystallized from ethanol. Thus the product attained was light pink in color. Melting point was 203 to 204 ^{o}C and the yield percentage was 85%.

Preparation of 2-(1H-Benzo[d]imidazol-2-yl)-1-phenyl-1H-benzo[f]chromen-3-amine (II):

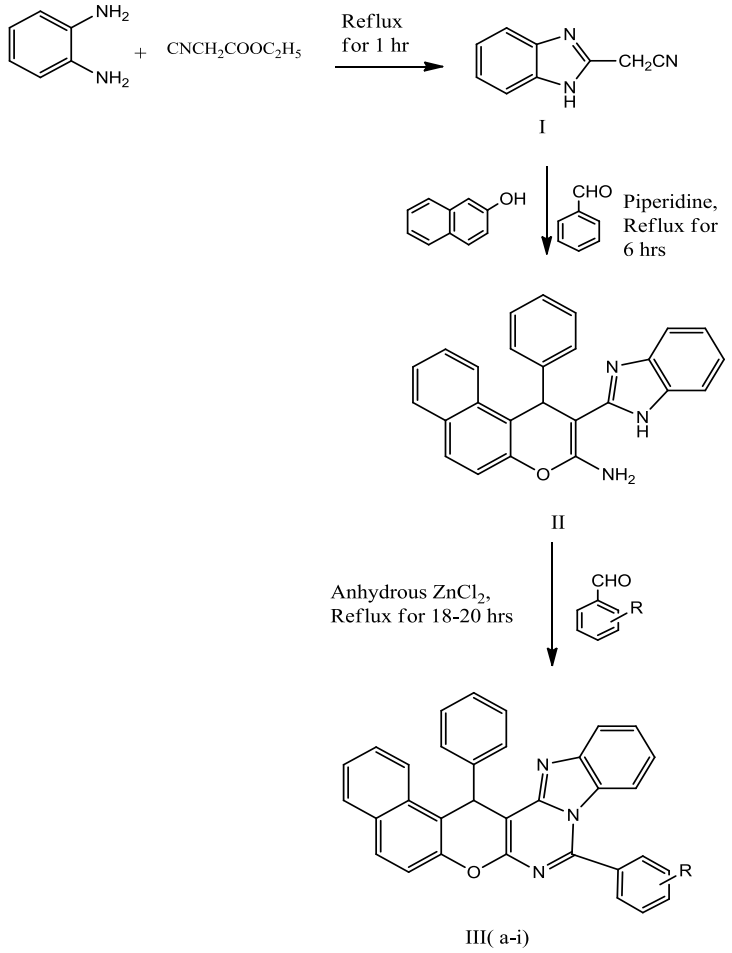
2-(1H-benzo[d] imidazol-2-yl acetonitrile (15.6gm, 0.1mol), Benzaldehyde (10.6 gm, 0.1mol) and naphthalene-2-ol (14.4 gm, 0.1mol) in ethanol (80 ml) was treated with piperidine (1ml) and refluxed for 6 hours. The solid thus separated was filtered, washed with ethanol and dried. Aqueous acetone was used to recrystallize the product. Thus the product so obtained

was light green color. Melting point 211 to 213^{o}c and percentage yield was 81%.

Preparation of 9,16-diphenyl-16H-benzo[4,5]imidazo[1,2-c] benzo[5,6]chromeno[3,2-e]pyrimidine (III a):

To a mixture of 2-(1H-benzo[d]imidazol-2-yl)-1-phenyl-1H-benzo[f]chromen-3-amine (3.89gm, 0.01mol) and Benzaldehyde (1.06 gm, 0.01 mol) in 50 ml of ethanol, 100 mg of anhydrous zinc chloride was added and refluxed for 6 to 8 hours. The reaction mixture was poured in to crushed ice and was kept in refrigerator overnight. The separated solid was then filtered and dried. The product was recrystallized from ethanol, percentage of yield was 82%, melting point 207-209^{o}C.

The remaining compounds of this series from III b to III i were synthesized by using the same procedure as described for III a. Figure-1 shows the scheme for synthesis of substituted derivatives.



III- R = a = H ,b = 4- Cl, c =2- Cl , d = 4- N $(CH_3)_2$, e = 2- NO_2

f = 2-OCH_3, g = 3,4,5-OCH_3, h= 2-OH, i =4-OH.

Fig. 1: Scheme for Synthesis of Benzimidazole fused Benzopyran derivatives

Anti-bacterial activity:

All the compounds synthesized in the present investigation were screened for their anti-bacterial activity by exposing the compounds to standard procedures. Antibacterial activities were tested on nutrient medium against Bacillus Pumilus, Bacillus subtilis, Staphylococcus aureus, Escheria coli and Pseudomonas aeruginosa which are representative types of gram positive and gram negative organisms respectively. The antibacterial activity of the compounds was evaluated by disc-diffusion method [11, 12].

Method of testing:

The sterilized media was cooled to 45^{0}c with gentle shaking for uniform cooling and then inoculated with 18-24 hrs old culture under aseptic conditions, mixed well by gentle shaking. This media was then poured into sterile Petri dishes (appropriately marked) and allowed to set. After solidification, all the Petri dishes were transferred to laminar flow unit. Then the discs which were previously prepared were carefully kept on the solidified media with the assistance of sterilized forceps. These Petri dishes were kept for one-hour diffusion at room temperature and then incubated at 37^{0}c for 24 hours in an incubator.

The extent diameter of inhibition after 24 hours was estimated as the zone of inhibition in millimeters and the results were recorded.

RESULTS AND DISCUSSION

The proposed derivatives were synthesized and physical and chemical characteristics were studied and

recorded as shown in table 1, table2 and figures 2,3,4,5,6and 7. The anti-bacterial potency of the synthesized derivatives was evaluated and recorded in table3 which demonstrates that the compound III-f was found to possess good activity. While the compounds III-d, III-g and III-h were found to exhibit moderate activities. Among the various compounds III-f showed good activity specifically against Gram-negative bacteria. This establishes the fact that benzopyrans can be a rich source for exploitation. Therefore, in search of new generation of active compounds, it may be worthwhile to explore the possibility in this area by fusing and substituting different groups and to increase the potency.

Table No. 1: Physical Characteristic data of Benzopyran derivatives

S.No.	Compound Code	Mol. Formula	Molecular Wt.	Solvent for Crystallization (Yield %)	Melting Point (^{0}c)
1	II	$C_{26}H_{19}N_3O$	389.45	Aq.acetone (81%)	211-213^{0}c
2	III a	$C_{33}H_{21}N_3O$	475.54	Ethanol (82%)	207-209^{0}c
3	III b	$C_{33}H_{20}ClN_3O$	509.98	Ethanol (66%)	194-196^{0}c
4	III c	$C_{33}H_{20}ClN_3O$	509.98	Ethanol (66%)	196-198^{0}c
5	III d	$C_{35}H_{26}N_4O$	518.21	Ethanol (72%)	182-184^{0}c
6	III e	$C_{33}H_{20}N_4O_3$	520.54	Ethanol (58%)	178-180^{0}c
7	III f	$C_{34}H_{23}N_3O_2$	505.57	Ethanol (70%)	188-190^{0}c
8	III g	$C_{36}H_{27}N_3O_4$	565.62	Ethanol (71%)	209-211^{0}c
9	III h	$C_{33}H_{21}N_3O_2$	491.54	Methanol (64%)	209-211^{0}c
10	III i	$C_{33}H_{21}N_3O_2$	491.54	Ethanol (66%)	211-213^{0}c

Table No. 2: Spectral data of Synthesized Benzopyran derivatives

C.Code	Chemical Shift (δ) in ppm		ESI-MS (m/z)
	^{1}H-NMR (DMSO d6)	^{13}C-NMR (DMSO d6)	
II	4.73 (s, 1H of CH), 5.21(s, 2H of NH_2), 7.12-8.33 (m, 15H, Ar-H), 9.23 (s, 1H of NH)	157.9, 151.8, 141.5, 140.1, 138.9, 133.3, 129.2, 128.3, 126.2, 123.1, 122.1, 118.9, 115.2, 88.8, 34.3	390.1
III b	4.89 (s, 1H of CH), 6.85-8.56 (m, 19H, Ar-H);	171.3, 161.1, 153.3, 144.1, 143.3, 141.3, 135.1, 134.3, 132.6, 129.3, 128.1, 126.2, 123.1, 120.3, 118.9, 115.4, 112.3, 42.2	510.3
III d	3.06 (s, 6H of $-(NCH_3)_2$), 4.89 (s, 1H of CH), 6.82-8.55 (m, 19H, Ar-H);	171.9, 161.1, 155.3, 153.6, 144.1, 143.3, 141.3, 135.1, 133.5, 132.7, 129.3, 128.4, 126.2, 123.1, 120.3, 118.7, 115.2, 112.3, 42.7, 41.3	519.2
III f	3.83 (s, 3H of CH_3) 4.97 (s, 1H of CH), 6.83-8.51 (m, 19H, Ar-H);	171.5, 161.1, 157.2, 153.7, 144.1, 143.4, 141.3, 135.3, 133.5, 131.7, 129.3, 128.4, 126.2, 123.1, 120.3, 118.9, 116.7, 115.1, 112.3, 56.1, 42.2	506.3
III h	4.91 (s, 1H of CH), 5.35 (s, 1H of OH), 6.87-8.59 (m, 16H, Ar-H);	171.6, 162.3, 154.3, 153.6, 144.1, 143.3,141.3, 135.1, 133.5, 130.6, 129.3, 128.3, 126.1, 123.1, 120.3, 118.9, 115.2, 43.9	492.1

II-2-(1H-Benzo[d]Imidazol-2-yl)–1-phenyl-1H-benzo[f]chromen-3-amine; III-b-9-(4-chlorophenyl)-16-phenyl-16H-benzo[4,5]imidazo[1,2-c] benzo[5,6]chromeno[3,2-e]pyrimidine; III-d-N,N-dimethyl-4-(16-phenyl-16H-benzo[4,5]imidazo[1,2-c]benzo[5,6]chromeno[3,2-e]pyrimidin-9-yl)aniline; III-f-9-(2-methoxyphenyl)-16-phenyl-16H-benzo[4,5]imidazo[1,2-c]benzo[5,6]chromeno[3,2-e]pyrimidine; III-h-2-(16-phenyl-16H-benzo[4,5]imidazo[1,2-c]benzo[5,6]chromeno[3,2-e]pyrimidin-9-yl-phenol.

Table No. 3: Anti-Bacterial Activity of Synthesized derivatives

Sample Code	*Inhibition zone diameter in mm									
	S.aureus		B.subtilis		B.Pumilis		E.coli		P.aureginosa	
	50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg
III a	-	-	5	11	3	10	5	12	-	-
III b	6	12	4	13	5	12	6	14	6	13
III c	5	10	5	10	5	9	4	10	7	11
III d	9	17	8	17	10	18	9	20	10	19
III e	5	12	5	13	7	15	6	13	6	14
III f	10	19	9	19	10	20	10	20	10	21
III g	8	16	7	17	11	20	10	20	9	18
III h	7	16	7	16	8	19	9	19	8	18
III i	6	15	5	15	7	17	6	18	7	16
Gentamycin	13	19	12	17	15	20	13	24	15	25
Ampicillin	15	23	14	24	13	23	14	22	14	23
DMF	-	-	-	-	-	-	-	-	-	-

Average of triplicate ± Standard deviation; DMF- Dimethyl Formamide

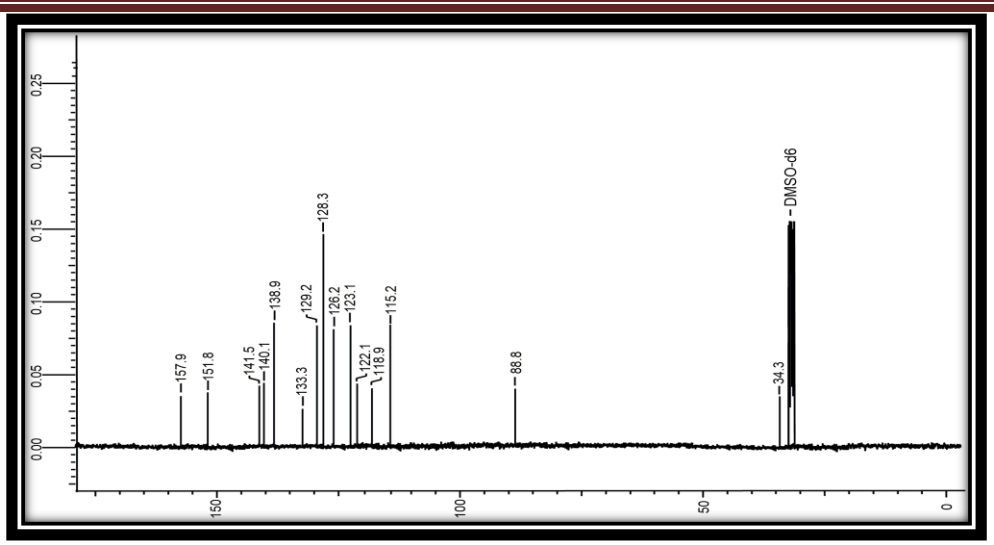


Fig. 2: ^{13}C NMR spectra of compound II

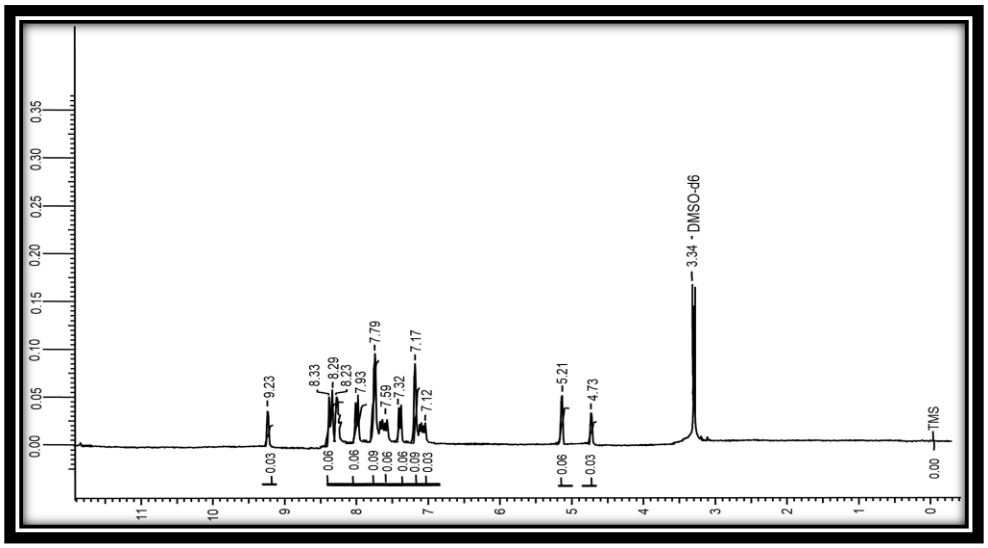


Fig. 3:^{1}H NMR spectra of compound II

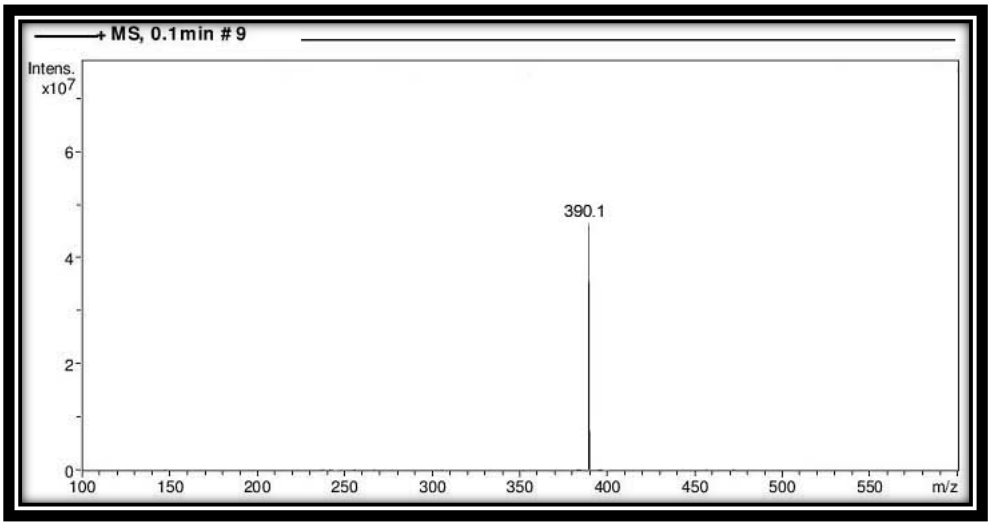


Fig. 4: Mass spectra of compound II

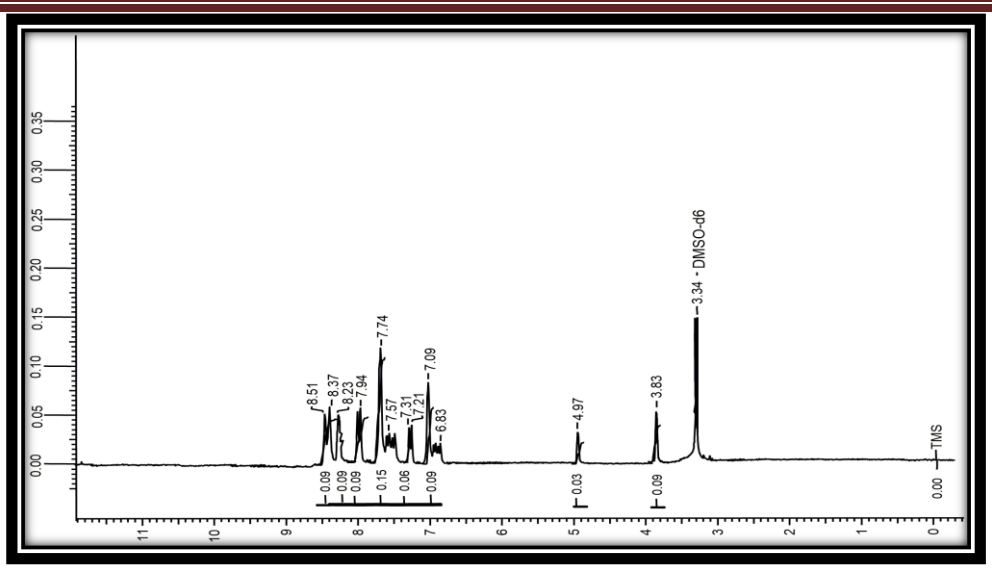


Fig. 5:^{13}C NMR spectra of compound III f

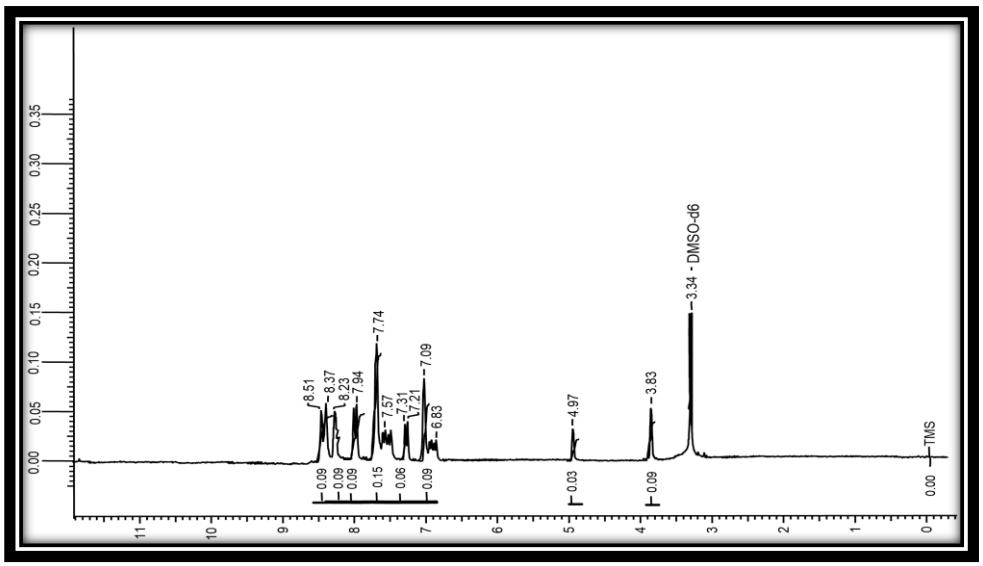


Fig. 6:^{1}H NMR spectra of compound III f

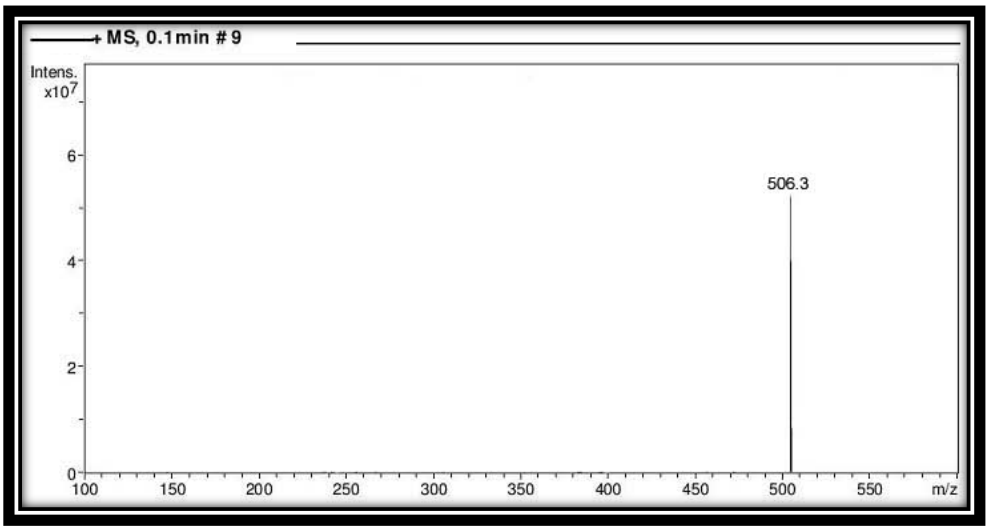


Fig. 7: Mass spectra of compound III f

CONCLUSION

In the present study, the two systems such as substituted benzopyrans and benzimidazole are connected to one another and demonstrates very powerful, more specific less toxic antibacterial agent. This combination is expected to result in a significant increase in potency.

As expected, benzopyran derivatives displayed antibacterial activity in which some are good and modestly active than the standard employed for examination. Accordingly a detailed study of toxicity is required. Further molecular modeling may give better drugs.

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