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SYNTHESIS AND SCREENING OF SUGAR HYDRAZINO BENZOTHIOZOLYL THIOCARBAMIDE FOR BIOLOGICAL STUDIED

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Abstract: Benzothiazoles are bicyclic ring system with multiple applications. The synthesis of novel glycosides derivatives and investigation of their chemical and biological behavior have gained more importance in recent decades. Serial of Hepta-*O*-acetyl- β -D-maltosyl-3-(2)-hydrazino-1,3-Substituted Benzothiazolyl thiocarbamides has been synthesized by the interaction of two pharmacophores, hepta-*O*-acetyl- β -D-maltosyl isothiocyanate and substituted 2-hydrazino-1,3-benzothiazoles in acetone medium. The reaction mixture was kept at room temp for 24 hrs. Acetone is evaporated then product is recrystallized by petroleum ether (60-80%). Benz-fused compounds have been employed in the synthesis of various compounds which show very potential pharmacological activities. Carbohydrate is the key element in variety of biological phenomena and its *N*-linked sugar derivatives also exhibit wide range of medicinal activities. Keeping in this view, when one biological active molecule is linked to another, the resultant molecule generally has increased potency. The identities of these newly synthesised Hepta-*O*-acetyl- β -D-maltosyl-3-(2)-hydrazino-1,3-Substituted Benzothiazolyl thiocarbamides have been established on the basis of usual chemical transformations and IR, ¹H NMR and Mass spectral studies. The antibacterial and antifungal activities of also reported. Some of these derivatives exhibit significant antimicrobial activity. These compounds show appreciable activity towards these microorganisms like *Escherichia coli*, *Proteus vulgaris*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Aspergillus Niger* and *Candida albicans*.

Keywords: 2-hydrazino-1,3 benzothiazole , substituted benzothiazolyl thiocarbamide, hepta-*O*-acetyl- β -D-maltosyl isothiocyanate, Biological studies.



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INTRODUCTION

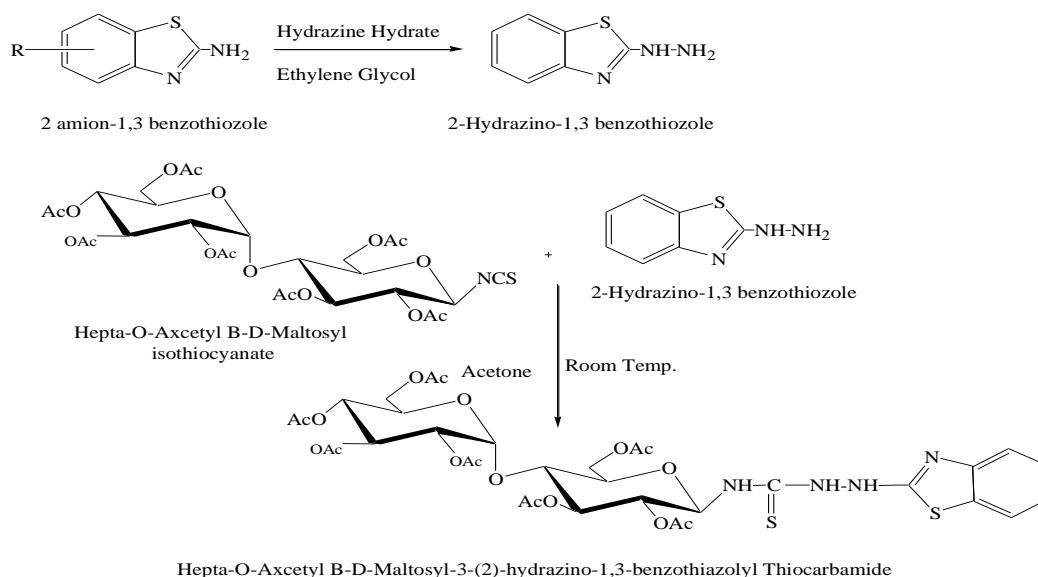
Benzothiazoles constitute an importance's class of compounds. In recent year heterocyclic compound analogues and derivatives have attracted strong interest due to their useful biological and pharmacological properties. Benzothiazole, a multifaceted nucleus, has been under research for the last two decades. Being a heterocyclic compound, benzothiazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Its aromaticity makes it relatively stable, although as a heterocycle, it has reactive sites which allow for functionalization¹. From the literature survey, it has been found that extensive work has been reported on 2-substituted benzothiazole derivatives in past and evaluated for different activities like antibacterial¹, anticancer², antiviral³, antitumor⁴, antifungal⁵, antiinflammatory⁶, antioxidative and radioprotective⁷, antidiabetic^{8,9}, anthelmintic¹⁰, anti-leishmanial¹¹, anticonvulsant¹², neuroprotective¹³, a topical carbonic anhydrase inhibitor and an antihypoxic. Taking this into view, and in continuation of our search for biologically potential benzothiazole derivatives, a certain new derivatives were synthesized taking benzothiazole as the basic moiety. The *N*-lactosylated compounds also have been known for their great biological importance. They have been found use as diuretic agents, analgesics, antidiabetic compounds, bacteriostatic agents and some remarkable significant activities¹⁴. Different benzothiazoles react with hydrazine and this hydrazino benzothiazoles then focused to fuse with *N*-lactosylated compound¹⁵. Hence, in present work, different benzothiazoles react with hydrazine and this hydrazino benzothiazoles then focused to fuse with *N*-maltosylated compound.

Results and discussion

Herein, we report the synthesis of various Hepta-*O*-acetyl- β -D-maltosyl-3-(2)-hydrazino-1,3-Substituted Benzothiazolyl thiocarbamides **III(a-g)** by interaction of Hepta-*O*-acetyl- β -D-maltosyl- isothiocyanate (**I**) and substituted 2-hydrazino-1,3-benzothiazole **II(a-g)** in acetone medium. All products were crystallized from ethanol before recording the physical data (Table-1). The purity of compounds was checked by TLC. The spectral analysis¹⁵⁻¹⁷ IR, ¹H NMR and Mass spectra of the product were observed. Optical rotation of the product was also recorded.

III (a-g) (Scheme-II).

Scheme for synthesis shown as follows:



Where, R= (a) Phenyl, (b) *o*-tolyl, (c) *m*-tolyl, (d) *p*-tolyl, (e) *o*-Cl-Phenyl, (f) *m*-ClPhenyl, (g) *p*-Cl-Phenyl And Ac= Acetyl

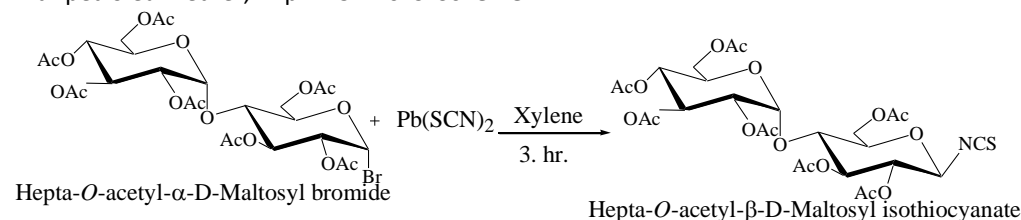
Experimental

Material and Methods

All chemicals were research grade. Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450 cm^{-1}) spectrophotometer. ^1H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in CDCl_3 solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Thin layer chromatography (TLC) was performed on silica Gel G and spots were visualized by iodine vapour. The compounds were screened for their antibacterial and antifungal activities by the disc diffusion assay method [18]. The compounds describe in this paper were first time synthesized by the multistep reaction protocol.

1] Preparation of hepta-O-acetyl- β -D-Maltosyl- isothiocyanate:^[19]

To the suspension of hepta-O-acetyl- α -D-maltosyl bromide (21g) in sodium dried xylene (80ml) was added lead thiocyanate (15gm). The reaction mixture was refluxed gently for 3 hrs. with frequent shaking. The solution then cooled and librated lead bromide was removed by filtration. The xylene filtrate was then treated with petroleum ether (60-80 $^\circ\text{C}$) with stirring, a pale yellow solid obtained (12 gm). This solid was expected hepta-O-acetyl- β -D-maltosyl isothiocyanate. It was purified by dissolving it in a minimum quality of chloroform and reprecipitating with petroleum ether, m.p. 115-120 $^\circ\text{C}$. **Scheme I**



2] Preparation of 2- hydrazino-1,3-benzothiozole

a) Preparation of benzothiozole

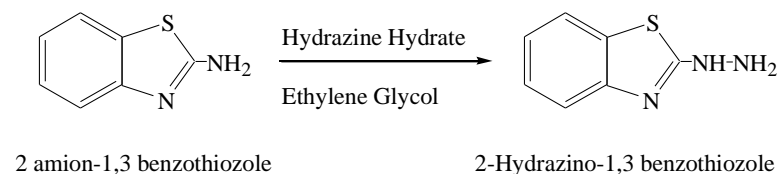
The required substituted benzothiazoles has been prepared by the oxidative cyclization of aryl thiocarbamide with the help of molecular bromine To the chloroformic paste of phenyl thiocarbamide (5gm in 10ml) molecular bromine (20%) was added gradually with constant stirring until a slight excess of bromine was added as evident from an orange red colour. It was then allow to stand for 5 to 6 hrs. to resultant acidic solid was treated with cold ethanol, the solid dissolved in ethanol. On basification with dilute ice cold NH_4OH 2-aminobenzothiozole was separated out as a white solid (3gm). M.p. 130 $^\circ\text{C}$.

b) Preparation of 2- hydrazino-1,3-benzothiozole

Concentrated HCl (1mL) was added drop wise to hydrazine hydrate (0.2 M, 1mL 80%) at 5-10 $^\circ\text{C}$ followed by ethylene glycol (20mL). To the above solution 2-aminobenzothiazole (0.01 M, 1.85g) was added in portions. It was then refluxed for 3 h, cooled and poured onto crushed ice. The separated solid was filtered, dried and recrystallized from ethanol.

II(a-g). (Scheme-II)

Scheme 2:



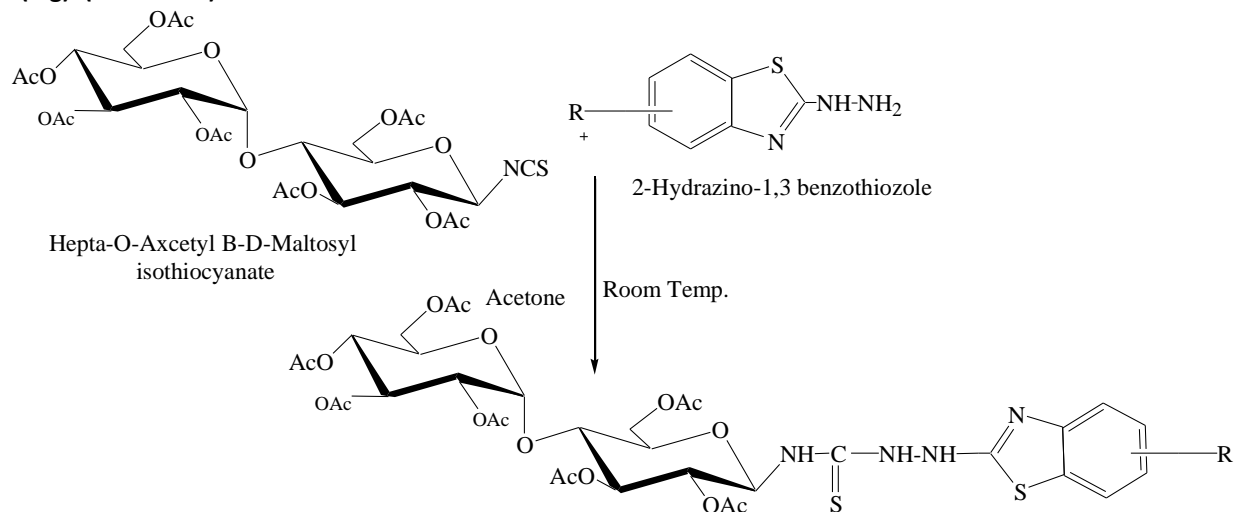
2 amion-1,3 benzothiozole

2-Hydrazino-1,3 benzothiozole

3] Preparation of 1- Hepta-O-acetyl-β-D-maltosyl-3-(2)-hydrazino-1,3-Substituted Benzothiazolyl thiocarbamides

A acetone solution of hepta-O-acetyl-β-D-maltosyl isothiocyanate (0.025M, 2.5g in 20mL) was mixed with acetone solution of 2-hydrazino-1,3-benzothiazole (0.025M, 0.37g in 10mL), and mixture after shaking for some time was kept at room temperature for 24 h. Acetone was distilled off to obtained sticky residue. This residue was triturated several times with petroleum ether to afford a light coloured solid.

III(a-g). (Scheme-III).



Where, R= (a) Phenyl, (b) *o*-tolyl, (c) *m*-tolyl, (d) *p*-tolyl, (e) *o*-Cl-Phenyl, (f) *m*-ClPhenyl, (g) *p*-Cl-Phenyl And Ac= Acetyl

3a: IR (KBr): ν 3444.87 (N-H), 3057.17 (Ar-H), 1747.51 (C=O), 1629.85 (C=N), 1136.07 (C=S), 939.33 (Characteristics of maltose), 783.10 (C-S), ¹H NMR (δ in ppm, CDCl₃): δ 5.58-5.21 (4H, s, N-H), 2.11-1.22 (21H, s, aliphatic protons), 5.24-2.14 (14H, m, maltosyl proton), Mass (m/z): 772 (M⁺), 753, 619, 237, 167.5; Anal. Calcd for C₃₄H₄₄O₁₇N₄S₂: C, 48.34; H, 5.21; N, 6.63; S, 7.58; Found: C, 49.00; H, 5.20; N, 6.60; S, 7.50.

On the basis of all above facts the product with m. p. 90°C was assigned the structure 1- Hepta-O-acetyl-β-D-maltosyl-3-(2)-hydrazino-1,3-Substituted Benzothiazolyl thiocarbamid. When the reaction of hepta-O-acetyl-β-D-maltosyl isothiocyanate. was extended to several other 2- hydrazino-1,3-benzothiazole corresponding Hepta-O-acetyl-β-D-maltosyl-3-(2)-hydrazino-1,3-Substituted Benzothiazolyl thiocarbamid has been synthesized.

3b: IR (KBr): ν 3448.87 (N-H), 3017.17 (Ar-H), 1707.51 (C=O), 1620.85 (C=N), 1127.07 (C=S), 940.33 (Characteristics of maltose), 785.10 (C-S), ¹H NMR (δ in ppm, CDCl₃): δ 5.50-5.61 (4H, s, N-H), δ 2.13-1.20 (21H, s, aliphatic protons), δ 2.24-2.50 (14H, m, maltosyl proton), Mass (m/z): 772 (M⁺), 753, 619, 237, 167.5; Anal. Calcd for C₃₅H₄₆O₁₇N₄S₂: C, 48.85; H, 5.36; N, 6.52; S, 7.45; Found: C, 48.80; H, 5.40; N, 5.50; S, 7.40.

On the basis of all above facts the product with m. p. 85°C was assigned the structure 1- Hepta-O-acetyl-β-D-maltosyl-3-(2)-hydrazino-1,3-Substituted (*o*-tolyl) Benzothiazolyl thiocarbamid.

Table -1: Physical data for characterization of compounds (3a-g)

Compd	Yield %	R _f	M.P. °C	Analysis (%): Found (calcd)	
				N	S
3a	55.00	0.46	90	6.60(6.63)	7.50(7.58)
3b	60.00	0.67	85	5.50 (6.52)	7.40(7.45)
3c	78.00	0.58	95	6.60 (6.52)	7.42(7.45)
3d	65.00	0.69	120	6.63(6.52)	7.48(7.45)
3e	76.00	0.62	87	6.30(6.37)	7.30(7.28)
3f	80.00	0.59	110	6.35(6.37)	7.35(7.28)
3g	69.00	0.70	128	6.40(6.37)	7.32(7.28)

C and H analysis was found satisfactory in all cases.

Antimicrobial Studies

All the compounds have been screen for both antimicrobial and antifungal activity using cup plate agar diffusion method¹⁸⁻²⁰ by measuring the inhibition zone in mm. the compounds were taken at a concentration of 1 mg/mL using Dimethyl Sulphoxide (DMSO) as solvent. Amikacin (100 µg/mL) was used as standard for antibacterial activity and Fluconazole (100 µg/mL) as standard for antifungal activity. The compounds were screen for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Klebsiyella species* by using Nutrient Agar medium and antifungal activity against *Trichoderma harzianum* and *Verticillium species* was determined by using Potato Dextrose Agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized cotton swab. After inoculation the well was punched by using sterile stainless steel cork borer of 6mm diameter. In to these wells were added 0.1 mL portion of the test compounds in solvent. The drug solution was allowed to diffuse for an hour into the medium. The plate was incubated at 37°C for 24 h and 30°C for 48 h for antibacterial and for antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured. The results are presented in Table 2. Antibacterial studies of these compounds indicated that compounds exhibited most significant activity against All the other compounds exhibited low to moderate activity. (Table2)

Sr. no	<i>E. c.</i>	<i>S. a.</i>	<i>P. v.</i>	<i>P. a.</i>	<i>S. t.</i>	<i>K. p.</i>	<i>A. n.</i>	<i>C. a.</i>
1(3a)	17	20	20	19	18	21	19	20
2(3b)	10	19	15	12	20	19	20	21
3(3c)	18	14	19	17	15	18	17	19
4(3d)	14	20	18	18	19	20	20	19
5(3e)	16	--	16	--	12	--	22	18
6(3f)	10	10	20	10	10	12	18	22
7(3g)	--	12	18	14	08	17	21	--
Amikacin	18	21	23	19	20	21		
Fluconazole							24	24

Sample	Disc content	Resistant	Intermediate	Sensitive
Amikacin	100ug/ml	≤ 15 mm	16-20 mm	≥ 21 mm
Fluconazole	100ug/ml	≤ 15 mm	16-20 mm	≥ 21 mm

Conclusion

Derivatives were synthesized and characterized for their structure elucidation. As outline in synthesis process, important novel -1,3- substituted benzothiazolyl thiocarbamide has been synthesized. All the structure of the above compounds was in good agreement with Spectral and Analytical data. Various chemical and spectral data supported the structures. Some of the compounds synthesized showed promising antimicrobial activities. The newly synthesized thiocarbamides exhibits comparable antibacterial and antifungal activities against the organisms tested. The method adopted in this investigation is simple, efficient and inexpensive and is useful in synthesizing pharmacologically important molecules.

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References:

1. Bhawsar SB, Mane DV, Sinda DB, Shingare MS, Deokate AS and Congwane LV. Synthesis of some 8-[6'-substituted-1', 3'-benzothiazol-2'-yl) amino methyl] substituted hydroxyl coumarins and Evaluation of their antibacterial activity. Indian J Het Chem 1996; 8: 23.
2. Suvarna K, Swain SP and Gandhi AM. Synthesis and Evaluation of Novel Benzothiazole Derivatives against Human Cervical Cancer Cell Lines. Indian J Pharm Sci 2007; 69: 46-50.
3. Nagarajan SR, De CGA, Getman DP, Lu HF, Sikorski JA, Walker JL et al. Replacement of the ureas moiety by benzothiazolesulfonamide provided inhibitors of HIV-1 protease with improved potency and antiviral activities. Bioorg. and Med Chem Lett 2003;11: 4769.
4. Wells G, Bradshaw TD, Diana P, Seaton A, Shi DF, Westwell AD et al. Synthesis and Anti-tumor activity of Benzothiazole Substituted Quinol Derivatives. Bioorg Med Chem Lett 2000; 10: 513-515.
5. Latrofa A, Franco M, Lopodota A, Rosato A, Carone D and Vitali C. Structural modification and antimicrobial activity of *N*-cycloalkylidene-2, 3-dihydro-1, 3-
1. Ghayalkar *et. al.*, Am. J. PharmTech Res. 2012; 2(3) ISSN: 2249-3387 www.ajptr.com 1108
2. benzothiazoles, *N*-cycloalkyl-2-acylalkylidene-2, 3-dihydro-1, 3-benzothiazoles. IL Farmaco 2005; 60: 291-297.
6. Dogruer DS, Unlu S, Sahin MF and Yesilada E. Synthesis of (2-benzothiazolone-3-yl and 2-benzothiazolone-3-yl) acetic acid derivatives and Evaluation of their Antinocioceptive and Anti-inflammatory Activity. IL Farmaco 1998; 53: 80.
7. Cressier D, Prouillac C, Hernandez P, Amourette C, Diserbo M, Lion C, Rima G. Synthesis, antioxidant properties and radio protective effects of new benzothiazoles and thiadiazoles. Bioorg Med Chem 2009; 17: 5275.
8. Pattan SR, Suresh C, Pujar VD, Reddy VVK, Rasal VP and Koti BC. Synthesis and antidiabetic activity of 2-amino [5' (4-sulfonylbenzylidene)-2, 4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole. Indian J Chem 2005; 44B: 2404-2408.
9. Moreno DH, Villalobos MR, Ortiz AR, Diaz CD, Medina J.L, Webster S.P, Estrado SS, Ibarra BM, Leon RI, Navarrete VG. Antidiabetic activity on *N*-(6-substituted-1, 3-benzothiazol-2-yl) benzenesulfonamides. Bioorg Med Chem Lett 2008; 18: 2871-2877.
10. Barde AR, Barsu HK and Bobade AS. Synthesis of 5, 6-Disubstituted-2-(Substituted Phenyl Carboxamido) Benzothiazoles as Potential Anthelmintic and Anti-Microbial agents. Indian Drugs 1998; 35(9): 554-557.
11. Tapia RA, Prieto Y, Pautet F, Domard M, Sarciron ME, Walchshofer N, and Fillion H. Synthesis and Antileishmanial Activity of Indoloquinones Containing a Fused Benzothiazole Ring. Eur J Org Chem 2002; 17: 4005-4010.
12. Siddiqui N, Rana A, Khan SA, Haque SE, Alam MS and Ahsana W. Anticonvulsant and Toxicity Evaluation of Newly Synthesized 1-[2-(3,4-disubstituted phenyl)-3-chloro-4-oxoazetid-1-yl]-3-(6-substituted-1,3-benzothiazol-2-yl)ureas. Acta Chim Slov 2009; 56: 462-469.

13. Danzeisen R, Schwalenstoecker B and Gillardon F, Targeted antioxidative and neuroprotective properties of the dopamine agonist pramipexole and its nondopaminergic enantiomer SND919CL2x [(+)-2-amino-4,5,6,7-tetrahydro-6-L-propylamino-benzothiazole dihydrochloride]. *J Pharmacol Exp Ther* 2006; 316(1): 189–199.
14. Silverstein RM and Webster FX, "Spectrometric Identification of Organic Compounds", 6th ed., John Wiley and Sons, Inc, New York; 2011.
15. Ghayalkar *et al.*, Synthesis And Antimicrobial Activity Of Hepta- O-Benzoyl-B-D-Lactosyl-3-(2)-Hydrazino-1, 3-Benzothiazolyl Thiocarbamides. *Am. J. PharmTech Res.* 2012; 2(3), 2249-3387.
16. Williams DH and Fleming I, "Spectroscopic Methods in Organic Chemistry", 5th ed., Tata McGraw-Hill; 2004.
17. Dyer JR, "Applications of Absorption Spectroscopy of Organic Compounds", PHI Learning Private Limited, New Delhi; 2010.
18. Kawangh F, *Analytical Microbiology*, Academic press, New York; 1963.
19. British pharmacopoeia-II, Biological assay and Tests, The Stationary Office Ltd., London; 1998: A-205.
20. Kumar VMMJ, Jayadevaiah KV, Nagaraj TS, Jayachandran E, Bharathi DR Sreenivasa GM *et al.*, Synthesis, characterization and antimicrobial activity of new N-substituted-3-chloro-2-azetidinones. *Arch Pharm Sci Res* 2009; 1(1): 31-29.