Synthesis and biologically important of 2-mercaptobenzthiazole (MBT)-clubbed Chalcone derivatives

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ABSTRACT. In this present work base catalyzed method used for formation of Chalcone of (E)-4-(3-(4-hydroxyphenyl)acryloyl)-5-methyl-2(*p*-tolyl)-1H-pyrazol-3(2H)-one (**II**) reacted with derivatives of S-benzo[d]thiol-2-yl-2-chloroethanethioate (**I_{a-f}**) resulted in formation of corresponding derivatives of (E)-S-benzo[d]thiazol-2-yl 2-(4-(3-(5-methyl-3oxo-2(*p*-tolyl)-2,3-dihydro-1H-pyrazol-4-yl)-3-oxoprop-1-en-1-yl)phenoxy)etanethioate(**III_{a-f}**) was confirmed by spectral characterization such as IR, ¹H NMR, LC-MS and elemental analysis. The compounds were screened for their antimicrobial properties against a broad panel Gram-positive and Gram-negative bacteria as well as fungi.

1. INTRODUCTION

1,3-Diaryl-2-propen-1-ones, commonly known as chalcones are prominent secondary metabolites and precursors of flavonoids and is flavonoids in plants, these compounds are usually prepared by base or acid catalyzed aldol condensation between aromatic aldehydes and ketones under the homogeneous condition. . They serve as starting material for the synthesis of a variety of heterocyclic compounds that are of physiological significance. Because of their different functionalities, these compounds confer biological activities, such as synthons for the production of fiveandsix-member ring systems [1,2] for example Pyrazoles [3],Pyrazolines [4], isoxazolines [5], aurones [6], pyrimidine [7],falvanones [8] and di-aryl cyclohexenones [9]. The biological activities of chalcones are equally wide ranging. In fact, not many structural templates can claim association with such a diverse range of pharmacological activities, among which antimicrobial [10], anti-leishmanial [11], anti-malarial [12], antifungal [13], anti-viral [14], anti-inflammatory [15], cytotoxicity [16], anti-tumor [17], nematocidal [18] and anti-oxidant [19] are widely cited.

There are numerous biologically active bicyclic molecules containing two hetero atoms. 2-Mercaptobenzothiazole (MBT) is an important scaffold known to be associated with several biological activities, and its derivatives are manufactured worldwide for a wide variety of applications S-acetylhydrazide hydrazine [20], S-acyl [21]. MBT and their derivatives have attracted much attention of chemists and pharmacologists because of their broad spectrum of biological activities and applications as antifungal and antibacterial activities [22], fungicide, insecticide, sensitizer, and anti-scorching agent [23].

In the present communication, we report here a series of hybrid heterocyclic scaffolds by clubbing chalcone with 2-Mercaptobenzothiazole (MBT)[24], in the present study. The structures of the various synthesized compounds were assigned on the basis of infrared (IR), proton nuclear magnetic resonance spectroscopy (¹H-NMR) spectral data, and elemental analysis.

Step-1 Synthesis of derivatives of S-benzo[d]thiol-2-yl-2-chloroethanethioate (**I_{a-f}**)

- R = a) H d) -NH_2
 b) -CH_3 e) -NO_2
 c) -Cl f) F

Step-2 Synthesis of (E)-4-(3-(4-hydroxyphenyl)acryloyl)-5-methyl-2-(p-tolyl)-1H-pyrazol-3(2H)-one (**II**)

Step-3 Synthesis of titled compounds (**III_{a-f}**) **Scheme-1** Synthesis of compounds of (**III_{a-f}**)**2. RESULT AND DISCUSSION**

The synthetic route of the compounds is outlined in scheme-1. A series of titled compounds (**III_{a-f}**) were synthesized in three steps. Derivatives of S-benzo[d]thiol-2-yl-2-chloroethanethioate (**I_{a-f}**) was prepared by reaction between different benzothiazole-2-thiol (where, initially prepare by different 2-amino benthiozole and carbon di-sulphide with KOH in EtOH) with chloro acetyl chloride and K_2CO_3 IN DMF. Synthesis of (E)-4-(3-(4-hydroxyphenyl) acryloyl)-5-methyl-2(p-tolyl)-1H-pyrazol-3(2H)-one (**II**) were prepared by reacting 1H pyrazole containing acetaphenone with p-hydroxybenzaldehyde where NaOH was used as a base catalyst. This product (**II**) on reaction with the derivatives of (**I_{a-f}**) resulted in the formation of titled compounds (**III_{a-f}**) in good yield.

3. CHARACTERIZATION**IR spectra**

The IR spectra of the titled compound (**III_{a-f}**) (molecular formula $C_{29}H_{23}N_3O_5S_2$) has given a weak absorption stretching vibration band observed at 2753 cm^{-1} confirmed the presence of methylene group in the final product. A sharp intensified band at 1647 cm^{-1} proves the presence of carbonyl group in the structure. The presence of ($-C=C-$) in the aromatic ring was proved by absorbance at 1537 cm^{-1} . The carbonyl functional group present in vicinity to the Chalcone ($-CH=CH-$) has shown a sharp and intense absorption peak at 1669 cm^{-1} . Another stretching vibration at 1591 cm^{-1} in the spectra of compounds (**III_{a-f}**).

 H^1 NMR

H^1 NMR spectra observed for the compound under investigation exhibited several absorption peaks corresponding to desired protons. A peak appearing particularly at $\delta = 4.66$ confirmed the protons of methylene group in the final structure of aromatic rings. Also the appearing two broad peaks of two

doublets at $\delta=7.15$ and $\delta=7.88$ confirmed the presence protons of two carbon atoms each of the chalcone group. The proton belonging to aromatic rings of the final molecule were found to correspond between the δ values 7.08-8.93.

4. MATERIAL AND METHOD

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded by a perkin-Elmer 237 spectrophotometer and ^1H NMR was recorded in DMSO with TMS as internal standard on Bruker. AM 400. Mass spectra were recorded on M S route JMS 600-H. All the synthesized compounds were purified by recrystallization method. All the chemicals and solvents were A.R Grade and were used without further purification.

5. GENERAL PROCEDURE

Preparation of benzothiazole-2-thiol Substituted 2- amino thiophenol (0.01mol) was taken in R.B.F containing ethanol (40ml) and KOH (0.01mol), CS_2 (0.02mol) was added to the well-stirred solution and reflux for 12-15h. The ethanol was then distilled off and cooled to room temp. The content was poured into ice coldwater and acidifies with dilute HCL till the precipitates were obtained. The separated solid was washed with cold water and dried to get desired product. The formation of titled intermediate was confirmed by the TLC.

Step-1 Preparation of derivatives of S-benzo[d]thiol-2-yl-2-chloroethanethioate.

Take 2-marcapto benzthiazole (0.01mol) in 10ml DMF. Dissolve it and then add 0.3 to 0.5 gm K_2CO_3 & stir it for 15 min. Then add CAC (0.01 mol) drop wise at 0-5 c. & stir the mix for 2h. After completion of reaction pour the mix. In cold water & collect the product.

Step-2 Preparation of (E)-4-(3-(4-hydroxyphenyl) acryloyl)-5-methyl-2(*p*-tolyl)-1H-pyrazol3 (2H)-one (II)

A mixture of aromatic aldehyde (0.01mol) and 4-acetyl-3-methyl-1-(tolyl)-Pyrazole-5(4H)-one (0.01mol) in 95% ethanol (20ml) were mixed in round bottom flask and 10ml of 60% of aq. Sodium hydroxide solution added drop wise. Resulting mix was stirred for at 5-10°C, poured into crushed ice and acidified with dilute HCl. The formation of titled intermediate was confirmed by observing the TLC using ethyl-acetate: hexane as a mobile phase.

Step-3 Preparation of titled compound.

Take 0.01 (mol.) (E)-4-(3-(4-hydroxyphenyl)acryloyl)-5-methyl-2(*p*-tolyl)-1H-pyrazole(2H)-one dissolve in acetone. To this solution different derivative were added & K_2CO_3 (0.02mol) was added to the above mix. Then it was allowed to stir for 4hr at room temp. The completion of reaction was monitored using TLC plate using ethyl acetate: hexane as mobile phase.

3a. IR: 2890 cm^{-1} (C-H str. Of Ar.), 2753 cm^{-1} (methylene), 1663 & 1593 (-CH=CH- of Chalcone), 1537 cm^{-1} (-C=C- of Ar.), 1647 cm^{-1} (carbonyl group) Mass(m/z): 541.1(M^+)NMR: 2.12 & 2.20 (s, 3H), 4.66 (s, 2H, methylene), 7.15 & 7.88 (d, 1H), 7.08-8.93 (4H, d, Ar-H)

3b. IR: 2893 cm^{-1} (C-H str. Of Ar.), 2755 cm^{-1} (methylene), 1663 & 1593 (-CH=CH- of Chalcone), 1539 cm^{-1} (-C=C- of Ar.), 1645 cm^{-1} (carbonyl group) 2950-1370 (-CH₃)Mass(m/z): 555.07(M^+)NMR: 2.10 & 2.24 (s, 3H), 4.69 (s, 2H, methylene), 7.11 & 7.91 (d, 1H), 7.08-8.93 (4H, d, Ar-H)

3c. IR: 2891 cm^{-1} (C-H str. Of Ar.), 2753 cm^{-1} (methylene), 1661 & 1590 (-CH=CH- of Chalcone), 1531 cm^{-1} (-C=C- of Ar.), 1647 cm^{-1} (carbonyl group) 1075 (Ar C-Cl) Mass(m/z): 575.0(M^+)NMR: 2.09 & 2.20 (s, 3H), 4.64 (s, 2H, methylene), 7.18 & 7.86 (d, 1H), 7.08-8.93 (4H, d, Ar-H)

3d. IR: 2896 cm^{-1} (C-H str. Of Ar.), 2758 cm^{-1} (methylene), 1660 & 1593 (-CH=CH- of Chalcone), 1541 cm^{-1} (-C=C- of Ar.), 1645 cm^{-1} (carbonyl group) 3375 (-NH₂)Mass(m/z): 556.12(M^+)NMR: 2.17 & 2.26 (s, 3H), 4.72 (s, 2H, methylene), 7.21 & 7.88 (d, 1H), 7.11-8.96(4H, d, Ar-H)

3e. IR: 2886 cm^{-1} (C-H str. Of Ar.), 2749 cm^{-1} (methylene), 1667 & 1590 (-CH=CH- of Chalcone), 1540 cm^{-1} (-C=C- of Ar.), 1647 cm^{-1} (carbonyl group) 1535 (-N₂) Mass(m/z): 586.1 (M^+)NMR: 2.10 & 2.28 (s, 3H), 4.67 (s, 2H, methylene), 7.14 & 7.90(d, 1H), 7.11-8.91 (4H, d, Ar-H)

3f. IR: 2895 cm^{-1} (C-H str. Of Ar.), 2750 cm^{-1} (methylene), 1660 & 1591 ($-\text{CH}=\text{CH}-$ of Chalcone), 1535 cm^{-1} ($-\text{C}=\text{C}-$ of Ar.), 1648 cm^{-1} (carbonyl group) 1067 (Ar C-F) Mass(m/z): 559.1(M^+) NMR: 2.13 & 2.21 (s, 3H), 4.68 (s, 2H, methylene), 7.19 & 7.91 (d, 1H), 7.12-8.90 (4H, d, Ar-H)

Table-1 Analytical data and Elemental analysis of compounds 3 (a-e)

Compound	M.F	Yield (%)	m.p ($^{\circ}\text{C}$)	Elemental analysis							
				% C		% H		% N		% S	
				Found	Calc.	found	Calc.	Found	Calc.	found	Calc.
a	$\text{C}_{29}\text{H}_{23}\text{N}_3\text{O}_4\text{S}_2$ 541.11	70	189	64.29	64.31	4.30	4.28	7.77	7.76	11.82	11.84
b	$\text{C}_{30}\text{H}_{25}\text{N}_3\text{O}_4\text{S}_2$ 555.13	76	192	64.85	64.84	4.51	4.53	7.54	7.56	11.55	11.54
c	$\text{C}_{29}\text{H}_{22}\text{N}_3\text{O}_4\text{S}_2\text{Cl}$ 575.07	71	201	60.48	60.46	3.87	3.85	7.31	7.29	11.15	11.13
d	$\text{C}_{29}\text{H}_{24}\text{N}_4\text{O}_4\text{S}_2$ 556.12	68	187	62.55	62.57	4.36	4.35	10.04	10.06	11.50	11.52
e	$\text{C}_{29}\text{H}_{22}\text{N}_4\text{O}_6\text{S}_2$ 586.10	70	191	59.38	59.37	3.80	3.78	9.56	9.55	10.40	10.93
f	$\text{C}_{29}\text{H}_{22}\text{N}_3\text{O}_4\text{S}_2\text{F}$ 559.10	73	187	62.23	62.24	3.95	3.96	7.50	7.51	11.47	11.46

6. ANTIMICROBIAL ACTIVITY

A broad panel of microbes was used for testing the antibacterial and antifungal properties of the molecules synthesized. The samples were tested by standard protocols like micro-dilution method. Concentration of the test compounds were kept constant (500ppm) during all the experiments. The bacterial, fungal and yeast cultures were maintained on Nutrient-Agar, potato-dextrose-agar and YEDP culture –tubes respectively and were sub cultured every fortnight and stored at $0-5^{\circ}\text{C}$ temp. Anti-bacterial tests were carried against gram positive and gram negative bacteria. The anti-fungal tests were carried against two fungal strains *Saccharomyces* and *A. Niger*. Compound 3c and 3e showed good activity.

Compounds	E-Coli	B-subtilis	Saccharomyces	A. Niger
3a	62.5	125	125	250
3b	125	31.5	125	125
3c	125	125	250	250
3d	62.5	31.5	125	125
3e	125	62.5	250	250
3f	62.5	125	125	125

7. CONCLUSION

In the present work, all the titled compounds were synthesized by condensation of Chalcone with derivatives of 2-mercaptobenzthiazole. All the synthesized compounds were studied for antimicrobial activity. Compound 3c and 3e shows good activity. All the synthesized compounds were characterized by spectral data.

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References

- [1] A.A.H. Abdel-Rahman, A.E.S. Abdel-Megied, M.A.M. Hawata, E.R. Kasem, M.T. Shabaan, *Monatshefte für Chemie* 138 (2007) 889-897.
- [2] M. Kidwai, P. Misra, *Syn. Commun.* 29 (1999) 3237-3250.
- [3] S.K. Tambe, N.S. Dighe, S.R. Pattan, M.S. Kedar, D.S. Muamade, *Pharmacologyonline* 2 (2010) 15-19.
- [4] R. Gupta, N. Gupta, A. Jain, *Ind. J. Chem.* 49B (2010) 351-355.
- [5] T. Shah, V.J. Desai, *Serb. Chem. Soc.* 72 (2007) 443-449.
- [6] A. Detsi, M. Majdalani, C.A. Kontogiorgis, L.D. Hadjipavlou, P. Kefalas, *Bioorg. Med. Chem.* 17 (2009) 8073-8085.
- [7] A. Solankee, G. Patel, S. Solankee, *Oriental J. Chem.* 24 (2008) 1035-1038.
- [8] A. Kumar, S. Sharma, V.D. Tripathi, S. Srivastava, *Tetrahedron* 66 (2010) 9445- 9449.
- [9] J.S. Ghomia, M. Taheria, M.A. Ghasemzadeh, *Org. Prep. Proc. Int.* 42 (2010) 485-489.
- [10] R.C. Kamboj, R. Arora, G. Sharma, D. Kumar, C. Sharma, R. Joshi, K.R. Aneja, *Pharm. Chem.* 2 (2010) 157-170.
- [11] C. Reichwald, O. Shimony, S.N. Sacerdoti, C.L. Jaffe, C. Kunick, *Bioorg. Med. Chem. Lett.* 18 (2008) 1985-1989.
- [12] 11. Liu, M., Wilairat, P., & Go, L. M. *Journal of Medicinal Chemistry*, 44 (2001), 4443.
- [13] I. Karaman, H. Gezegen, M.B. Guerdere, A. Dingil, M. Ceylan, *Chem. Biodiver.* 7 (2010) 400-408.
- [14] T.T. Dao, P.H. Nguyen, H.S. Lee, E. Kim, J. Park, S.I. Lim, W.K. Oh, *Bioorg. Med. Chem. Lett.* 21 (2011) 294-298.
- [15] Y. Prasad, A. RajendraRao, R. SrinivasaRambabu, *Asian J. Chem.* 21 (2009)907-914.
- [16] J. Guzy, K.J. Vaskova, Z. Rozmer, K. Fodor, M. Marekova, M. Poskrobova, P. Perjesi, *FEBS Lett.* 584 (2010) 567-570.
- [17] 15. Miranda, C. L., Aponso, G. L. M., Stevens, J. F., Deinzer, M. L., & Buhler, D. R. *Journal of Agricultural and Food Chemistry*, 48 (2000), 3876
- [18] A. Saeed, O.B. Zachary, A. Hasan, G.L. Melissa, C.U. Alejandro, *Bioorg. Med. Chem.* 19 (2011) 2055-2073.
- [19] B.P. Bandgar, S.S. Gawande, R.G. Bodade, N.M. Gawande, C.N. Khobragade, *Bioorg. Med. Chem.* 17 (2009) 8168-8173.

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- [20] Khim Farm Zh. 18 (1984) 946–948.
- [21] Holbova E, Sidoova E, Zemanova M, Drobnicova *Chem. papers* 44 (1990) 363–368.
- [22] Lee JH, Kim JD. *Bull Korean Chem Soc.* 18 (1997) 442–443.
- [23] Ramadas K, Janarthanan N. *Synth Commun.* 29 (1999) 1003–1007.
- [24] Vijay Patil, Kalpna. Tilekar, Sonali Mehendole-Munj, Rhea Mohan, C.S. Ramaa *Eur. J. Med. Chem.* 45 (2010) 4539–4544.