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SYNTHESIS AND MICROBIAL ACTIVITY OF NOVEL CHROMENONE HETEROCYCLES BEARING BENZOTHIAZOLE MOIETY

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Abstract:
Chromenone Heterocycles bearing substituted benzthiazole groups have been synthesized *via* different synthetic practices. In present research work synthesis of the final Chromenone derivative was achieved in three steps: Acetylation of benzothiazole **1a-e** furnishes N-(benzo[d]thiazo-2-yl)acetamide **2a-e,**which on further condensation with substituted aromatic aldehydes yielded (E)-N-(benzo[d]thiazo-2-yl)cinnamide**3a-y.** The creation of final Chromenone derivative **4a-y** was carried out under Dean and Stark apparatus by cyclization of **3a-y** with Dimedone in presence of p-toluenesulphonic acid. Toluene used as a solvent in final step, was redistilled and used for the same reaction.

Keywords: Benzothiazole, Dimedone and Chromenone.

Introduction

Chromenones constitute an important class of heterocycles which possess potential biological and pharmacological properties. Structural features of various natural products include chromene moiety[1].These chromene heterocycles have proven antianalphylactic, anticoagulantspasmolytic, diuretic and anticancer properties[2-6].They also possess antiageing properties[7]. Recently, the anticoagulant, antibacterial, anti-helminthic, hypothermal and vasodilatory properties of chromene has been reviewed[8]. Moreover nitrogen and sulphur containing heterocycles continues to fascinate pharmacologists all over to explore various routes for synthesis of biologically important chromene derivatives. This prompted us to hunt for different strategies of synthesizing this compound. Herein we account on synthetic approaches to craft fused heterocyclic systems containing benzothiazole represented by compound **1** which are the precursor for the target product.

Results and Discussion

Spectral and elemental analysis confirmed the target molecule as 2-(6-substitutedbenzo[d]thiazo-2-yl)-7,8-dihydro-7,7-dimethyl-4-substitutedphenyl)-4H-chromen-5(6H)-one **4a-y** . The physical characterization data of synthesized compounds is given in **Table I**.

Further, the representative samples were screened for their antimicrobial evaluation against gram positive and gram negative bacteria. The synthesized compounds showed a promising activity against both. (**Table II**)
The pathway of synthesis of compounds **4a-y** is given in **SCHEME I**.

Experimental

Methods and Analysis

All chemicals procured (unless and until specified) were of the make E. Merck (Germany) and S. D. Fine Chemicals (India). Melting points (ºC) of all synthesized compounds were determined in open capillary tubes using Veego VMP-1 melting point apparatus and are uncorrected. The progress of the reaction was monitored by (TLC) thin layer chromatography and visualized under UV light. IR spectra were recorded from KBr pellets on Bruker ALPHA-T spectrophotometer (range of 4000-400 cm^{-1}). ^1H NMR spectra were recorded on JEOL AL 500MHz FTNMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard. C, H, N analyses were performed on Carlo Erba 1108 (C H N) Elemental Analyzer.

General Procedure:

A) Synthesis of *N-(6-substitutedbenzo[d]thiazo-2-yl)acetamide* (**2a-e)**

Acetic anhydride (0.05mole) was cooled to 10°C and 6-substitutedbenzo[d]thiazol-2-amine (0.01mole) **1** was added with constant stirring for of 5min, stirring was further continued for 2 hrs on magnetic stirrer. The reaction mixture was allowed to reach 25-30°C.Reaction mixture was quenched into ice cold water and the separated product was filtered, washed with 200ml of ice cold water and purified by recrystallization from a mixture of ethanol :water(1:4) (v/v) to yield **2a-e.**

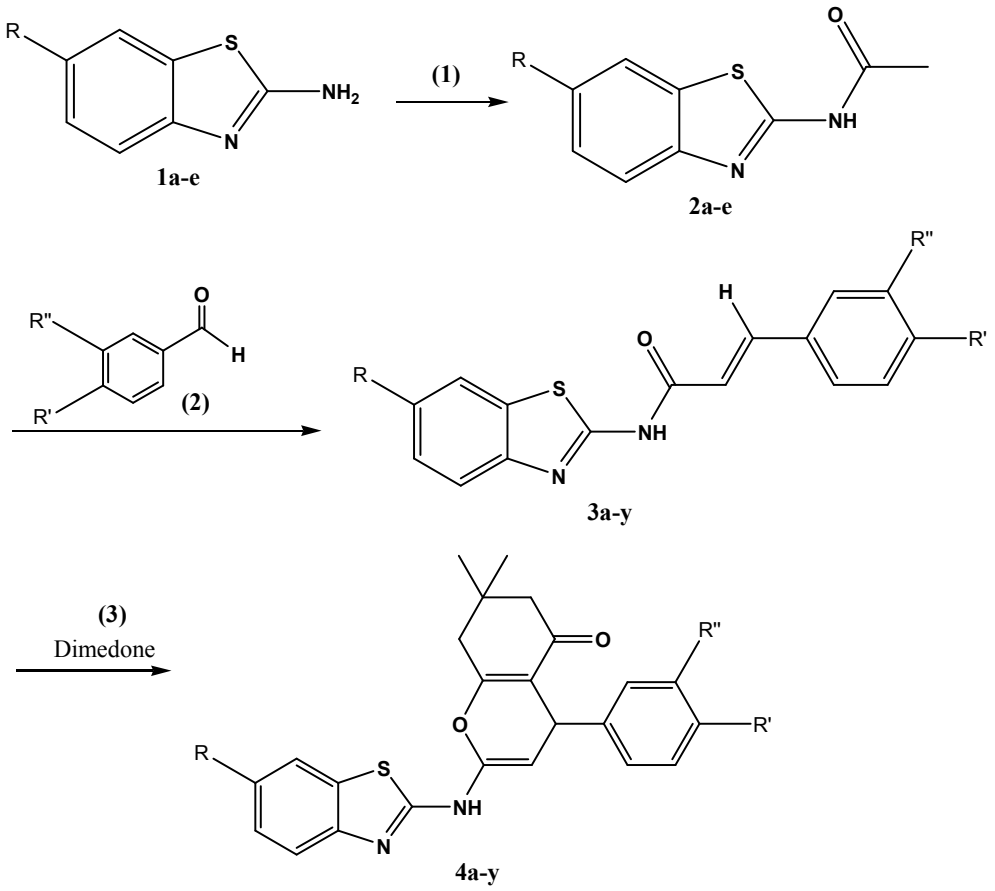
B) Synthesis of *N-(6-substitutedbenzo[d]thiazo-2-yl)cinnamide* (**3a-y)**

An equimolar mixture of compound **2a-e** and substituted aromatic aldehydes (0.01mole) was dissolved in 20cm^3 of absolute ethanol and was placed on a waterbath set at 70°C; 1cm^3 of 40% NaOH was added to the solution with constant stirring for 15min and then the stirring was further continued for 2 hrs at room temperature. Then 80cm^3 of ice cold water was added to the reaction mixture with constant stirring, precipitated product was filtered, washed with 100 cm^3 of ice cold water and purified by recrystallization with ethanol to yield **3a-y**.

C) Synthesis of *2-(6-substitutedbenzo[d]thiazo-2-yl)-7,8-dihydro-7,7-dimethyl-4-substituted phenyl)-4H-chromen-5(6H)-one* **(4a-y)**

An equimolar mixture of **3a-y** and Dimedone (0.01mole) was taken in a round bottom flask fitted with Dean and Stark apparatus, in the presence of *p*-toluenesulphonic acid (0.001mole) as a catalyst and toluene (40cm^3) as a solvent. The reaction mixture was stirred for 24 hrs at 110°C, then allowed to cool, the precipitated product was filtered and washed with ice cold water to yield **4a-y**.

Scheme I: Synthesis of compound 4a-y



Reaction Condition:**(1) Acetic Anhydride, 10^{o}C**
(2) 40%NaOH, EtOH
(3) Toluene, p-toluenesulphonicacid, Dean & Stark Apparatus

Spectral Analysis of the Representative Compound:

A) *2-(benzo[d]thiazol-2-ylamino)-7,8-dihydro-4-(4-methoxyphenyl)-7,7-dimethyl-4H-chromen-5(6H)-one*, **(4b)**

IR (cm^{-1}): 3310(NH stretching), 1710(C=O), 1540(C=N)

^{1}H NMR (500MHz, DMSO-d_6, δ ppm)**:** 1.13(s,6H, ×2CH_3), 1.90(s,2H, CH_2), 2.92(s,2H, CH_2), 3.78(s, 3H, OCH_3), 3.89(d,1H, CH) , 4.0(s,1H, NH), 4.2(d,1H, CH), 7.2-8.3(m, 8H, ArH).

^{13}C NMR (500 MHz, DMSO- d_6, ppm)**:** 26.71(2×CH_3), 34.58(CH), 46.36(CH_2), 49.58 (CH_2), 55.69(OCH_3), 73.24 (CH), 96.15 (Tetrahedral carbon), 114.25-152.60 (ArC and C=C), 155.10 &162.45(-C-O-C-), 174.52(C=N). 198.9(C=O)

C,H,N Analysis:**Calcd** $C_{25}H_{24}N_2O_3S$:**C**,69.42;**H**,5.59;**N,**6.48%.**Found C,**69.41;**H**,5.54;**N**,6.42%

B)*2-(benzo[d]thiazol-2-ylamino)-7,8-dihydro-4-(4-Hydroxy-3-methoxyphenyl)-7,7-dimethyl-4H-chromen-5(6H)-one,* **(4e)**

IR (cm^{-1}): 3295 (NH stretching), 1690(C=O), 1547(C=N)

^{1}H NMR (500MHz, DMSO-d_6, δ ppm)**:** 1.19 (s,6H, ×2CH_3), 1.98 (s,2H, CH_2), 2.87 (s,2H, CH_2), 3.88(s, 3H, OCH_3), , 3.96(s,1H, NH), 4.08 (d,1H, CH), 4.28(d,1H, CH), 4.76 (s,1H,OH), 7.06-8.14(m, 7H, ArH).
^{13}C NMR (500 MHz, DMSO- d_6, ppm)**:** 27.22(2×CH_3), 33.42(CH), 44.26(CH_2), 48.78 (CH_2), 55.89(OCH_3), 72.92 (CH), 97.05 (Tetrahedral carbon), 115.18-149.81 (ArC and C=C), 153.38 & 163.57 (-C-O-C-), 176.27(C=N). 196.24 (C=O).
C,H,NAnalysis:Calcd:$C_{25}H_{24}N_2O_4S$**:C**,66.96;**H**,5.35;**N**,6.25%.**Found:C**,67.10;**H**,5.42;**N**,6.36%

C) *2-(6-methylbenzo[d]thiazol-2-ylamino)-7,8-dihydro-4-(4-methoxyphenyl)-7,7-dimethyl-4H-chromen-5(6H)-one,* **(4g)**
IR(cm^{-1}): 3290 (NH stretching),1705(C=O),1555(C=N)
^{1}H NMR (500MHz, DMSO-d_6, δ ppm)**:**1.12 (s,6H, ×2CH_3), 1.87 (s,2H, CH_2), 2.48 (s,3H,CH_3), 2.78 (s,2H, CH_2), 3.67 (s, 3H, OCH_3) , 3.89 (s,1H, NH), 4.15(d,1H, CH), 4.35(d,1H, CH), 6.98-7.86 (m, 7H, ArH).
^{13}C NMR (500 MHz, DMSO- d_6, ppm)**:** 23.18 (CH_3), 27.22 (2×CH_3), 31.37(CH), 43.19(CH_2), 47.65 (CH_2), 55.67(OCH_3), 71.98 (CH), 96.65 (Tetrahedral carbon), 114.21-147.74 (ArC and C=C), 152.12 & 161.45 (-C-O-C-), 175.35(C=N). 197.28 (C=O).
C,H,N Analysis:**Calcd:**$C_{26}H_{26}N_2O_3S$:**C**,69.96;**H**,5.83;**N**,6.28%.**Found**:**C**,69.44;**H**,5.43;**N**,6.19%

D)*2-(6-methylbenzo[d]thiazol-2-ylamino)-7,8-dihydro-4-(4-hydroxyphenyl)-7,7-dimethyl-4H-chromen-5(6H)-one,* **(4h)**
IR(cm^{-1}): 3315(NH stretching),1695(C=O),1535(C=N)
^{1}H NMR (500MHz, DMSO-d_6, δ ppm)**:** 1.08 (s,6H, ×2CH_3), 1.74 (s,2H, CH_2), 2.35 (s,3H,CH_3), 2.71 (s,2H, CH_2), 3.89 (s,1H, NH), 4.22 (d,1H, CH), 4.39 (d,1H, CH),4.76 (s,1H,OH), 7.15-8.28 (m, 7H, ArH).
^{13}C NMR (500 MHz, DMSO- d_6, ppm)**:** 22.89 (CH_3), 26.97 (2×CH_3), 32.07(CH), 41.29(CH_2), 45.48 (CH_2), 72.87 (CH), 97.28 (Tetrahedral carbon), 117.48-146.97 (Ar-C and C=C), 153.73 & 162.57 (-C-O-C-), 173.87(C=N). 195.85 (C=O).
C,H,NAnalysis:**Calcd:**$C_{25}H_{24}N_2O_3S$:C,69.44;H,5.56;N,6.48%.**Found**:**C**,68.99;**H**,5.23;**N**,6.32%.

E) *2-(6-methoxybenzo[d]thiazol-2-ylamino)-7,8-dihydro-4-(4-hydroxyphenyl)-7,7-dimethyl-4H-chromen-5(6H)-one,* **(4m)**
IR(cm^{-1}): 3305 (NH stretching),1710(C=O),1570(C=N)
^{1}H NMR (500MHz, DMSO-d_6, δ ppm)**:** 1.12 (s,6H,2×CH_3), 1.93 (s,2H,CH_2), 2.88(s,2H, CH_2), 3.63 (d,1H, CH), 3.74 (s,3H,OCH_3), 4.02 (s,1H,NH), 4.17 (d,1H, CH), 4.84 (s, 1H,OH), 6.98-8.23 (m,7H,ArH).
^{13}C NMR (500 MHz, DMSO- d_6, ppm)**:** 25.55(2×CH_3), 31.75(CH), 42.36(CH_2), 48.56 (CH_2), 55.28(OCH_3), 71.89 (CH), 96.57 (Tetrahedral C), 114.25-152.60 (Ar-C and C=C), 155.10 &162.45(C-O-C),174.52(N=C-N), 196.76(C=O).
C,H,N Analysis:**Calcd**:$C_{25}H_{24}N_2O_4S$:C,66.96;H,5.35;N,6.25%,**Found**:**C,**65.96;**H**,5.11;**N**,6.10%.

F)*2-(6-methoxybenzo[d]thiazol-2-ylamino)-7,8-dihydro-4-(4-chlorophenyl)-7,7-dimethyl-4H-chromen-5(6H)-one,* **(4n)**
IR(cm^{-1}): 3265 (NH stretching),1725(C=O),1567(C=N)
^{1}H NMR (500MHz, DMSO-d_6, δ ppm)**:**1.16 (s, 6H, CH_3×2), 1.80 (s, 2H, CH_2),
2.77 (s, 2H, CH_2), 3.72 (d, 1H, CH), 3.93 (s, 3H. OCH_3), 4.15 (s, 1H, NH), 4.22 (d, 1H, CH), 7.15 -8.47 (m, 7H, ArH),

^{13}C NMR (500 MHz, DMSO- d_6, ppm)**:** 27.55(2×CH_3), 31.01(CH), 43.98(CH_2), 49.87 (CH_2), 55.73(OCH_3), 73.45 (CH), 97.56 (Tetrahedral C), 113.25-153.60 (ArC), 158.10 & 163.37 (-C-O-C-), 175.22(-N=C-N-), 199.26(C=O).
C,H,NAnalysis:**Calcd:**$C_{25}H_{26}N_2O_2SCl$:**C**,66.59;**H,**5.18;**N**,6.22%.**Found**:**C**,66.10;**H**,4.99;**N**, 6.09%

G)<u>*2-(6-chlorobenzo[d]thiazol-2-ylamino)-7,8-dihydro-4-(4-hydroxyphenyl)-7,7-dimethyl-4H-chromen-5(6H)-one,*</u> **(4r)**
IR(cm^{-1}): 3290(NH stretching),1690(C=O),1585(C=N)
^{1}H NMR (500MHz, DMSO-d_6, δ ppm)**:** 1.13 (s,6H, 2×CH_3), 1.86 (s,2H, CH_2), 2.89(s,2H,CH_2), 3.87(d,1H, CH), 4.08 (s,1H,NH),4.28 (d,1H,CH), 4.83(s,1H,OH), 7.08-8.26 (m, 7H,ArH),
^{13}C NMR (500 MHz, DMSO- d_6, ppm)**:** 27.45(2×CH_3), 31.65(CH), 44.56(CH_2), 49.85 (CH_2), 74.18 (CH), 96.89 (Tetrahedral C), 114.25-152.60(ArC),156.10 &161.45(-C-O-C-), 176.52(-N=C-N-). 199.9(C=O).
C,H,NAnalysis:**Calcd:**$C_{24}H_{21}N_2O_3SCl$:**C**,63.64;**H**,4.64;**N**,6.18%.**Found**:**C**,63.10:**H**,4.44;**N**, 5.98%

Anti Bacterial Evaluation

Representative compounds were evaluated for their antibacterial activity against gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* and gram-positive bacteria, *Streptococcus aureus*, and *Corynebacterium diphtheriae* using disc diffusion method [9-10]. The zone of inhibition was measured in mm and the activity was compared with the standard drug ciprofloxacin (broad spectrum antibiotic). The results of antibacterial screening studies are reported in **Table II**.

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Table I : Physical Characteristics of Compound 4a-y

Compounds	R	R'	R''	Molecular Formula	Yield (%)	m.p. (°C)
4a	-H	-H	-H	$C_{24}H_{22}N_2O_2S$	88	178-81
4b	-H	$-OCH_3$	-H	$C_{25}H_{24}N_2O_3S$	89	198-201
4c	-H	-OH	-H	$C_{24}H_{22}N_2O_3S$	92	187-90
4d	-H	-Cl	-H	$C_{24}H_{21}N_2O_2SCl$	87	212-15
4e	-H	-OH	$-OCH_3$	$C_{25}H_{24}N_2O_4S$	89	221-223
4f	$-CH_3$	-H	-H	$C_{25}H_{24}N_2O_2S$	87	241-243
4g	$-CH_3$	$-OCH_3$	-H	$C_{26}H_{26}N_2O_3S$	89	>250
4h	$-CH_3$	-OH	-H	$C_{25}H_{24}N_2O_3S$	82	189-92
4i	$-CH_3$	-Cl	-H	$C_{25}H_{23}N_2O_2SCl$	81	196-98
4j	$-CH_3$	-OH	$-OCH_3$	$C_{26}H_{26}N_2O_4S$	92	212-15
4k	$-OCH_3$	-H	-H	$C_{25}H_{24}N_2O_3S$	86	236-38
4l	$-OCH_3$	$-OCH_3$	-H	$C_{26}H_{26}N_2O_4S$	89	212-15
4m	$-OCH_3$	-OH	-H	$C_{25}H_{24}N_2O_4S$	89	201-04
4n	$-OCH_3$	-Cl	-H	$C_{25}H_{23}N_2O_2SCl$	84	223-25
4o	$-OCH_3$	-OH	$-OCH_3$	$C_{26}H_{26}N_2O_5S$	82	218-21
4p	-Cl	-H	-H	$C_{24}H_{21}N_2O_2SCl$	91	196-98
4q	-Cl	$-OCH_3$	-H	$C_{25}H_{23}N_2O_3SCl$	81	210-12
4r	-Cl	-OH	-H	$C_{24}H_{21}N_2O_3SCl$	87	195-97
4s	-Cl	-Cl	-H	$C_{24}H_{20}N_2O_2SCl_2$	84	222-24
4t	-Cl	-OH	$-OCH_3$	$C_{25}H_{23}N_2O_4SCl$	92	215-18
4u	-Br	-H	-H	$C_{24}H_{21}N_2O_2SBr$	80	218-220
4v	-Br	$-OCH_3$	-H	$C_{25}H_{23}N_2O_3SBr$	79	201-05
4w	-Br	-OH	-H	$C_{24}H_{21}N_2O_3SBr$	85	218-21
4x	-Br	-Cl	-H	$C_{24}H_{20}N_2O_2SClBr$	88	189-92
4y	-Br	-OH	$-OCH_3$	$C_{25}H_{23}N_2O_4SBr$	75	225-28

Table II. *in vitro* antibacterial activity of compound 4

Compound	Zone of inhibition (in mm)*			
	Gram Positive		Gram Negative	
	S.aureus	***C. diphtheria***	***E. coli***	***P. aeruginosa***
4b	17	18	17	17
4d	24	23	18	16
4i	21	20	20	20
4h	18	18	15	17
4m	23	20	17	15
4n	20	22	20	18
4p	23	21	18	17
4r	18	17	15	16
4s	24	23	23	20
4u	22	20	18	18
Ciprofloxacin(positivecontrol)	25	24	24	22
DMSO (negativecontrol)	0	0	0	0

- N.B. Concentration selected was 100 µg/ml and DMSO was used as the solvent