SYNTHESIS OF SOME NEW THIAZOLYL CHROMENONE DERIVATIVES BY USING α,α- DIBROMOKETONES

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Abstract

In organic synthesis, Thiosemicarbazide becomes one of the finest approach for the preparation of various heterocyclic compounds. Those reactions which contains C=O and C=N categories with thiosemicarbazide results in the composition of bioactive compounds specifically thiazoles. Hydrazine fragment contains a internal nitrogen centre which is the most softer nucleophilic centre as compared to effective absolute nitrogen, promotors allowing to nucleophillic replacement by the powerful nitrogen experienced cyclisation reaction to provide excellent yield of heterocycles under mild conditions. In the current study, some new derivatives of coumarin turned out to be formulated by treating "3-acetyl-2H-chromen-2-one" with hydrazinecarbothioamide subsequently cyclize with ethyl acetoacetate and then proceed with α,α- dibromoketones with the help of Hantzsch thiazole synthesis and to prepare other compounds and their pharmaceutical importance. All the compounds were identified by spectral details and physical evidence.

Paper Identification

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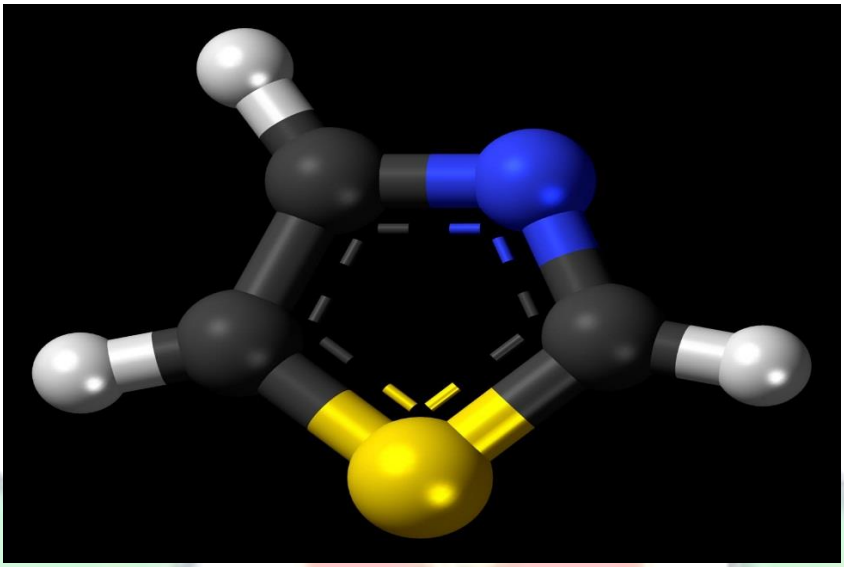
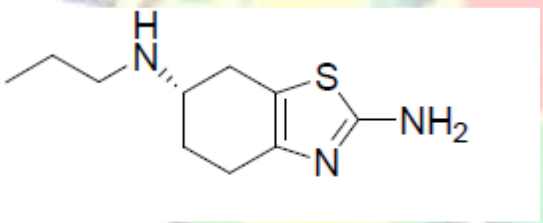
INTRODUCTION

Utilization of α,α Dibromoketones as systematized precursor for the preparation of heterocyclic compounds acquiring greater recognization due to their reliability and specificity throughout reactions.[1-13] In this investigation, α,α- Dibromoketones are operated for the establishment of thiazole nucleus implementing altered hantzsch thiazole synthesis (HTS)[14-19] . In the company of distinct synthetic procedures obtainable for the thiazoles . HTS is appreciably notable familiar appeal whichever comprises open chain reactants , α- functionalized carbonyl compounds (C-C) and thioamides to raise the nucleus". In modified HTS the utility of α,α Dibromoketones is considerable because in case of α- bromoketones due to low melting, lachrymosity and toxicity it is very difficult to handle. Thiazoles are one of the most prominent class of heterocyclic compounds which are existing in various natural products like thiamine pyrophosphate (TPP), carboxylase vitamin B1, penicillin and thiostrepton etc. In medicinal and pharmaceutical world, coumarins and thiazoles modified drugs have extensive effects on living matter such as antifungal, antiangiogenic, antibacterial and antipathogen applications. In synthetic organic chemistry, coumarin be the property of benzopyron group having cyclic lactone ring. In 1820, it was firstly detected by A.Vogel from tonka beans and sweet clover and termed as coumarin by Guibourt . In1869, for the first time it was prepared in the research laboratory by Perkin . The most intimate naturally available origin for coumarin are Tonka bean (Dipteryx odorata), Vanilla grass (Anthoxanthum odoratum) , Cassia (little coumarin), Sweet clover (Melilotus) etc . Shikimic acid pathway and Birch Donovan pathway are the major pathways for the preparation of coumarin.[20] The derivatives of coumarin happen extensively in umbellifereae, rutaceae, thymelaceae, and solanaceae etc.[21-22] Naturally and Synthetically available coumarins are the main source in therapeutic drug synthesis. These compounds contains pharmaceutical importance and grabbing anti – inflammatory,[23-24] anticoagulent[25], anti- tuberculosis, anti- fungal, anti – bacterial belongings[26-27]. Considering recent years, the synthesis of coumarin contains various forms of its derivatives. Their medicinal properties are based on their method of substitution. Many scientists have prepared coumarin build novel medicinal factor by virtue of molecular hybridization procedure which provide and magnificent chance for evolution of different compounds with excellent biological activity by combining various pharmacophores. The literature studies admit that coumarin exhibit anti-proliferative activity against neoplasm.[28] Various screening trials organized on these compounds exhibit optimistic activity resistant to different types of cancer like metastatic renal cell carcinoma, malignant melanoma, prostate cancer etc.[29-30] For all these advantages related to

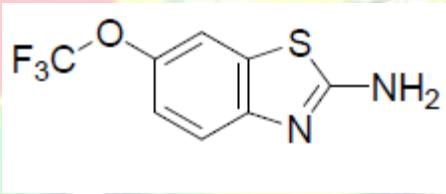
thiazoles and coumarin derivatives and following our work, we describe here the preparation of new library of thiazole derivatives from (E)-2-(1-(2-oxo-2H-chromen-3yl)ethylidene)hydrazinecarbothioamide



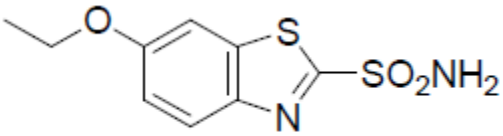
Structure of Thiazole



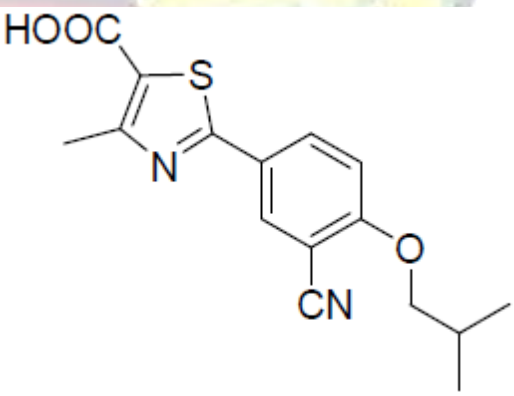
Pramipexole (dopamine D_2- agonist)



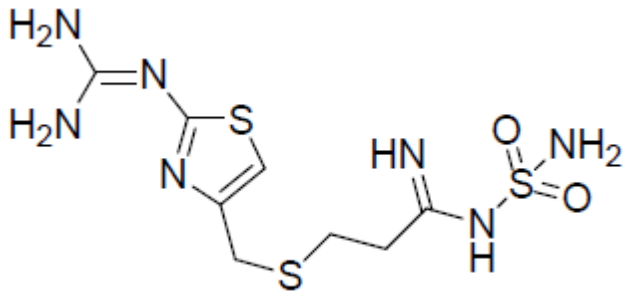
Riluzole (neuroprotective)



Ethoxzolamide (diuretics)



Febuxostat (xanthine oxidase inhibitor)

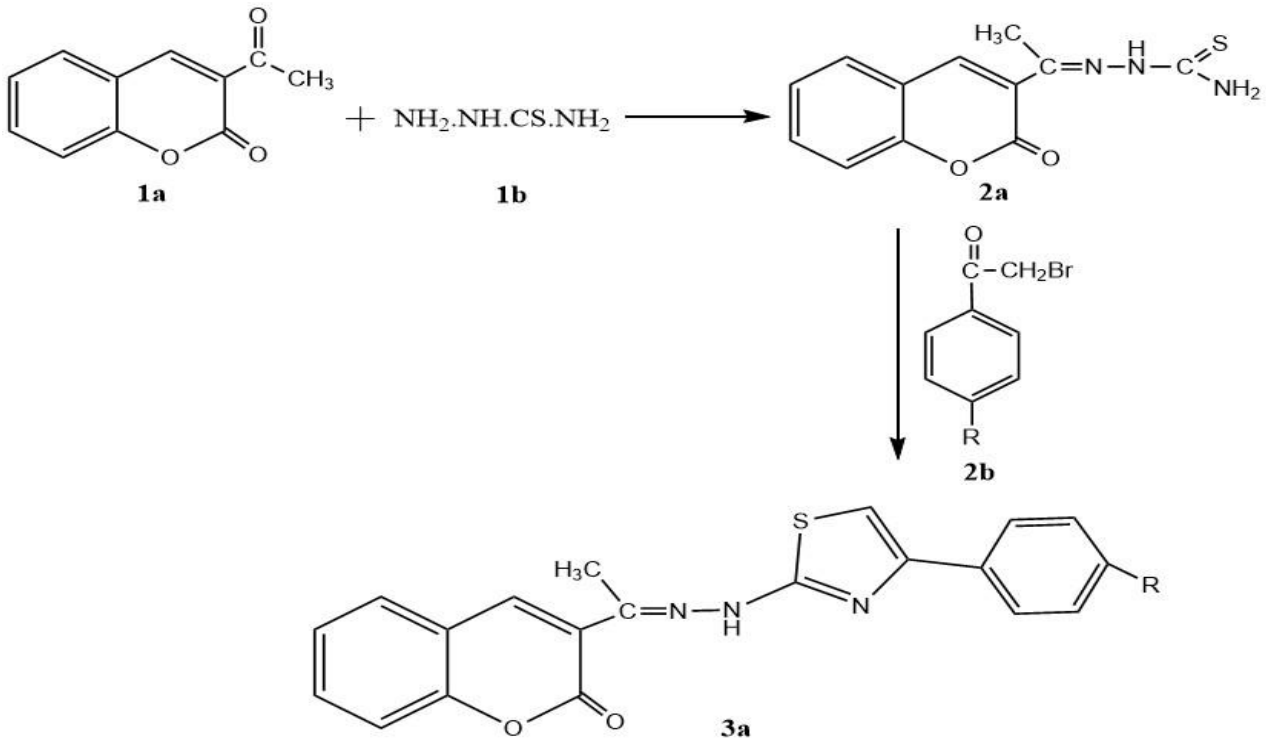


Famotidine (H_2 receptor antagonist)

Structure of drugs containing thiazole nucleus

RESULT AND DISCUSSION

Gradually , we begin our work with the treatment of substituted α,α-dibromoketones with (E)-2-(1-(2-oxo-2H-chromen-3yl)ethylidene)hydrazinecarbothioamide **(2a)** and the solvent used was ethanol while stirring at normal temperature . The reaction takes place according to assumption to synthesize the thiazole compound 3-(1-(2-(4-chloro phenyl) thiazol-2-yl) hydrazineylidene) ethyl)-2H-chromen-2-one (**3a)** with 80% yield. During the initial stage of reaction the reactants were completely soluble in solvent and after the completion of reaction a yellowish brown solid was obtained. Significantly, the reaction was executed with numerous substituted α,α-dibromoketones (**3b-3g)** to provide the comparable derivatives of thiazoles. The synthetic arrangement of (**3a)** was confirmed over evidence of spectral proof (NMR,IR) and elementary examination. The ^{1}H NMR range shows signals at δ 2.12 (s, 3H, CH_3), 7.19 (s, thiazolyl-H), 7.35- 8.16 (m, 8H, Ar-H), 8.45 (s, coumarinyl-H). The^{13}C NMR spectra display signals at δ 4.9, 105.4, 116.5, 118.6, 123.9, 125.8, 127.2, 128.3, 128.1, 128.8, 129.4, 129.7, 131.7, 133.9, 133.8 according to our assumption. By doing thin layer chromatography of the reaction mixture suggested the construction of solitary product. Regular workout of the reaction mixture subsequently purify the unrefined solid by recrystallization with ethanol and washing with water to obtain the pure form of thiazole derivatives. The same procedure is applied for the synthesis and purification of compounds **3b-3g.**



Where R = H, Cl, Br, NO_2, CH_3, F, OCH_3

SCHEME 1 - α, α-Dibromoketones reagent during preparation of various new thiazol-2-yl hydrazineylidene ethyl-2H- chromen-2-one.

TABLE 1 Physical data of thiazolylchromenones

COMPOUND	MOLECULAR FORMULA	MELTING POINT (˚c)	YIELD %
3a	$C_{20}H_{14}ClN_3O_2S$	170-171	80
3b	$C_{20}H_{14}BrN_3O_2S$	174-175	92
3c	$C_{21}H_{17}N_3O_3S$	168-169	88
3d	$C_{21}H_{17}N_3O_2S$	178-180	93
3e	$C_{20}H_{14}N_4O_4S$	194-195	85
3f	$C_{20}H_{15}N_3O_2S$	185-186	78
3g	$C_{20}H_{14}FN_3O_2S$	204-205	88

EXPERIMENTATION

The necessitate α,α-dibromoketones were incorporated on the report of publications procedure and characterized by comparing their melting point[31]. **(Boeykens, M.; Kimpe, N. D. Tetrahedron, 1994).** The required 3- acetyl coumarin for the present study was synthesized by stirring salicylaldehyde, ethylacetoacetate and piperidine for 5 min and enable to cool and yellow coloured solid was formed.[32] According to literature studies **Mahadi Ali et al**. and **Vekariya H.** synthesized (E)-2-(1-(2-oxo-2H-chromen-3 yl)ethylidene)hydrazinecarbothioamide **(2a)** on refluxing by adding glacial acetic acid and HCl as a stimulant but we synthesized it with modest moderation[32] . During its preparation, calculated amount of 3-acetyl coumarin (**1a)** and thiosemicarbazide **(1b)** was stirred and the solvent used was ethanol. After the achievement of reaction a yellow coloured solid product was drawned.[33]

All the solvents and the chemicals which were used during synthesis were of analytical research grade purchased from Spectrochem chemicals Ltd. (Mumbai, India). Time to time the accomplishment of the reaction was observed from analytical thin layer chromatography (TLC) by making use of Aluminium "Merck" TLC "silica gel plates".

Melting point measured on open capillary tubes on an "electrothermal apparatus and were left uncorrected". The instrument used for IR characterization was PerkinElmer spectrum IR version 10.6.2. All the NMR data were recorded on Bruker Avance NEO 500 MHz NMR spectrometer SAIF, P.U. and the solvent used was DMSO.

CHARACTERIZATION

3-(1-(2 -(4-"chlorophenyl)thiazol-2-yl)"hydrazineylidene)ethyl)-2H-chromen-2-one"" (3a)

Yellowish brown Powder, M.pt.170-171 ˚C.

IR (ν_{max}, KBr): 1719 (C=O), 3487 (N-H), 1672 (C=N).

^{1}H NMR (DMSO-d_6 500MHz): δ 2.12 (s, 3H, CH_3), 7.19 (s, thiazolyl-H), 7.35-8.16 (m, 8H, Ar-H) , 8.45 (s, coumarinyl- H).

^{13}C NMR (DMSO-d_6 500MHz): δ 4.9, 105.4, 116.5, 118.6, 123.9, 125.8, 127.2, 128.3, 128.1, 128.8, 129.4, 129.7, 131.7 ,133.9, 133.8, 150.6, 153.4, 155.8, 159.6, 1713.

Anal. Calculated for $C_{20}H_{14}ClN_3O_2S$: C, 60.69; H, 3.58; S, 8.12; Found: C, 60.79; H, 3.78; S, 8.07;

Molecular wt.: 395.05. m/z: 395.12, 397.13, 397.11.

3-(1-(2-(4-Bromophenyl)thiazol-2-yl) hydrazineylidene)ethyl)-2H-chromen-2-one (3b)

Dark brown powder ; M.pt.174-175˚C.

IR (ν_{max}, KBr): 1748 (C=O), 3457 (N-H), 1645 (C=N).

^{1}H NMR (DMSO-d_6 500MHz): δ 2.12 (s, 3H, CH_3), 7.34-7.78 (m, 8H, Ar-H), 7.39 (s, thiazolyl-H), 8.47(s, coumarinyl-H).

^{13}C NMR (DMSO-d_6 500MHz): δ 4.9, 105.5, 116.6, 118.8, 123.3, 123.6, 125.5, 127.2, 128.4, 128.1, 128.3, 132.5, 132.7, 132.0, 133.3, 150.5, 153.7, 155.4, 159.3, 171.6.

Anal. Calculated For $C_{20}H_{14}BrN_3O_2S$: C, 54.59; H, 3.25; S, 7.20; Found: C, 54.75; H, 3.13; S, 7.02;

Molecular wt.: 440.32 m/z: 439.07, 441.09, 442.5

3-(1-(2-(4-methoxyphenyl)thiazol-2-yl) hydrazineylidene)ethyl)-2H-chromen-2-one" (3c)

Dark yellow Powder ; M.pt.168-169˚C

IR (ν_{max}, KBr): 1733 (C=O), 3475 (N-H), 1669 (C=N).

^{1}H NMR (DMSO-d_6 500MHz): δ 2.12 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 7.18 (s, thiazolyl-H), 7.15-7.78 (m, 8H, Ar-H) , 8.42 (s, coumarinyl-H").

^{13}C NMR (DMSO-d_6 500MHz): δ 4.9, 55.6, 105.6, 114.8, 114.9, 116.9, 118.6, 123.7, 125.4, 125.8, 127.2, 128.3, 128.6, 128.3, 133.8, 150.2, 153.7, 155.3, 159.7, 160.5, 171.4.

Anal: Calculated For $C_{21}H_{17}N_3O_3S$: C, 64.47; H, 4.30; S, 8.18; Found C, 64.57; H, 4.26; S, 8.00;

Molecular wt.: 391.45 m/z: 391.24, 392.22, 393.15.

3-(1-(2-(4-p-tolyl) thiazol-2-yl")hydrazineylidene) ethyl)-2H-chromen-2-one (3d)

Light brown Powder; M.pt. 178-180 ˚C.

IR (ν_{max}, KBr): 1723 (C=O), 3476 (N-H), 1658 (C=N).

^{1}H NMR (DMSO-d_6 500 MHz): δ 2.25 (s, 3H, CH_3) , 2.28 (s, 3H, CH_3), 7.19 (s, thiazolyl-H), 7.36-7.78 (m , 8H, Ar-H), 8.19 (s, coumarinyl-H).

^{13}C NMR (DMSO-d_6 , 500MHZ): δ 4.4, 21.9, 105.6, 116.8, 118.9, 123.8, 125.9, 125.6, 125.8, 127.4, 128.6, 129.9, 129.9, 130.5, 131.0, 133.6, 150.8, 153.3, 155.7, 159.9, 171.7.

Anal: Calculated for $C_{21}H_{17}N_3O_2S$: C, 67.19; H, 4.58; S, 8.57; Found C, 66.93; H, 4.49; S, 8.47;

Molecular wt.: 375.45 m/z: 375.24, 376.26, 377.33.

3-(1-(2-(4-nitrophenyl)thiazol-2-yl) hydrazineylidene)ethyl)-2H-chromen-2-one (3e)

Bright yellow powder ; M.pt.194-195˚C.

IR (ν_{max}, KBr): 1767 (C=O), 3446 (N-H), 1640 (C=N).

^{1}H NMR (DMSO-d_6 500 MHz): δ 2.12 (s, 3H, CH_3) , 7.24 (s, thiazolyl-H), 7.35-8.39 (m, 8H, Ar-H), 8.44 (s, coumarinyl-H).

^{13}CNMR(DMSO-d_6 500 MHz): δ 10.5, 105.7, 116.5, 118.4, 123.7, 124.9, 124.4, 125.7, 126.3, 126.5, 127.8, 128.6, 133.4, 139.5, 147.9, 150.6, 153.7, 155.6, 159., 171.5.

Anal: Calculated For $C_{20}H_{14}N_4O_4S$: C, 59.15; H, 3.49; S, 7.85; Found: C, 59.34; H, 3.37; S, 7.69;

Molecular wt.: 406.42. m/z: 406.19, 407.19, 408.15

3-(1-(2-(4-phenylthiazol-2-yl) hydrazineylidene)ethyl)-2H-chromen-2-one (3f)

Mustard yellow powder; M.pt.185-186˚c.

IR (ν_{max}, KBr): 1758 (C=O), 1652 (C=N), 3445 (N-H).

^{1}H NMR (DMSO-d_6 500MHz): δ 2.13 (s, 3H, CH_3), 7.34-7.75 (m , 8H, Ar-H), 7.39 (s, thiazolyl-H), 7.57 (s, Aryl-H), 8.47 (s, coumarinyl-H).

^{13}CNMR(DMSO-d_6 500MHz): δ 4.9, 105.5, 116.4, 118.7, 123.4, 125.8, 127.9, 127.5, 127.5, 128.7, 128.4, 129.3, 129.3, 133.8, 133.5, 150.5, 153.6, 155.3, 159.7, 171.4.

Anal: Calculated For $C_{20}H_{15}N_3O_2S$: C, 66.49; H, 4.16; S, 8.84; Found C, 66.69; H, 4.05; S, 8.67;

Molecule wt.: 361.42. m/z: 361.15, 362.17, 363.16

3-(1-(2-(4-fluorophenyl)thiazol-2-yl) hydrazineylidene)ethyl)-2H-chromen-2-one (3g)

Rust brown powder; M.pt.204-205˚c.

IR (ν_{max}, KBr): 1728 (C=O), 3467 (N-H), 1663 (C=N)

^{1}H NMR (DMSO-d_6 500MHz): δ 2.13 (s, 3H, CH_3), 7.34-7.78 (m, 8H, Ar-H), 7.39 (s, thiazolyl-H), 8.43 (s, coumarinyl-H).

^{13}C NMR (DMSO-d_6 500MHz): δ 4.9, 105.7, 116.5, 116.7, 116.8, 118.9, 123.8, 125.4, 127.4, 128.5, 128.6, 130.7, 130.5, 133.4, 150.6, 153.8, 155.9, 159.8, 162.7, 171.3.

Anal: Calculated For $C_{20}H_{14}FN_3O_2S$: C, 63.34; H, 3.75; S, 8.47; Found: C, 63.43; H, 3.65; S, 8.27;

Molecular wt.: 379.41 m/z: 379.16, 380.18, 381.19

CONCLUSION

The reaction examined in this work specifically signify the prominence of thiazoles in medicinal chemistry . On the basis of coumarin derivatives various biologically active compounds have been acquired. So, our synthesized compounds would be immense rich in pharmacological activities and to investigate their biological activity will be our future prospective which further will be more useful in medicinal world.

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