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Research Article

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Synthesis and characterization of some 1,4-diazepines derivatives

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ABSTRACT

Synthesis of new compounds possessing 7-membered rings with two heteroatom a 1,4-diazepines having fused heterocyclic ring of coumarin and thiophene and cyclic secondary amine as a side chain. Substituted 8-amino-10-methyl chromeno [3, 4-b] thieno [2, 3-e] [1, 4] diazepin-6(12H)-one hydrochlorides treated with cyclic secondary amine (N-methyl, N-ethyl, N-phenyl and N-benzylpiperazine) in potassium carbonate and toluene at reflux condition.

Keywords*:* 1, 4-diazepines, substituted, cyclic secondary amine.

INTRODUCTION

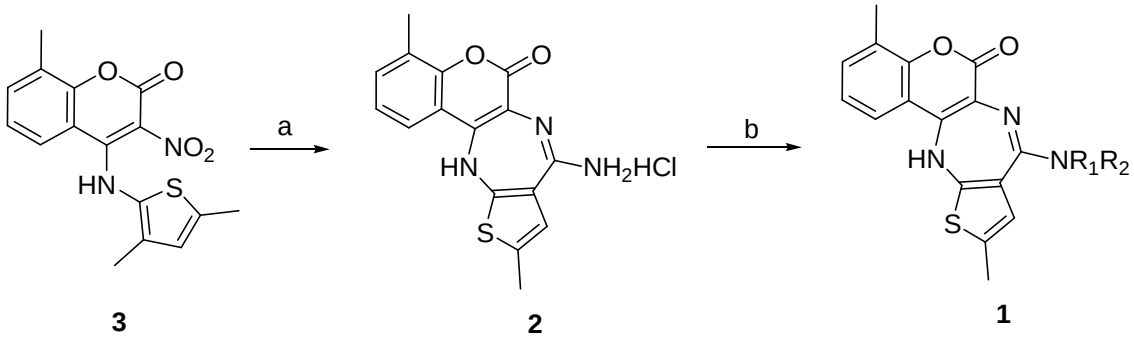
The clinical importance and commercial success associated with the 1,4- benzodiazepine class of central nervous system (CNS)-active agents and the utility of 1,4-diazepines as peptidomimetic scaffolds have led to their recognition by the medicinal chemistry community as privileged structures. This ring system has demonstrated considerable utility in drug design, with derivatives demonstrating a wide range of biological activities. On the other hand, examples of the serendipitous discovery of new drugs based on an almost random screening of chemicals synthesized in the laboratory are striking. Since 1960, when chlordiazepoxide (Librium) entered in the market, efforts to discover new biologically active compounds with limited side effects in benzodiazepines are going on which are reflected by the important number of publication focused in this subject [1-5].

Among all types of benzodiazepines (1, 2; 1, 3; 1, 4; 1, 5; 2, 3; & 2, 4) only 1, 4 and 1, 5-benzodiazepines have found wide applications in medicines, during one of the most important classes of the therapeutic agents with wide spread biological activities [6] including hypnotics, sedatives, anxiolytics and antianxiety etc., effect range from their well-documented anticonvulsive or tranquilizing properties, through pesticidal [7] or antitumor [8] action and to their more recently described peptidomimetic activity [9]. The cyclic amidines represent an important functional group in medicinal chemistry and can be found in many natural products or FDA-approved drugs, *e.g.* the antipsychotic clozapine and loxapine. Moreover, substituted amidines are useful intermediates in the synthesis of many heterocyclic compounds [10]. The most common and convergent strategies for amidine synthesis are based on the addition of amines to activated amide intermediates, *e.g.* imido ester [11], imidoyl chloride [12] or *o*-triflated imidate [13]. In 1969, Fryer *et al* reported a one-step method for the preparation of cyclic amidines from amides using titanium tetrachloride complex [14]. Clozapine was originally synthesized in 1960s by Sandoz-Wander Ltd based upon a structural similarity to the tricyclic antidepressant, but it showed unexpectedly a high antipsychotic activity that lead to a new class of antipsychotic drug useful in the treatment of schizophrenia.

Different synthetic pathways are generally used to convert lactams or aminoesters into the amidine group. The diazepines were synthesized by reacting the corresponding diazepinone derivatives with an appropriate amine in the presence of $TiCl_4$ and anisole according to modified Fryer's method [15]. The diazepinones were also converted into the corresponding thiones that after reaction with an amine gave the desired amidine. Oxa- and thiazepine analogues were obtained following another approach. Lactams were treated with an excess of phosphorus oxychloride in

refluxing toluene to give iminochlorides which directly reacted with an excess of the desire amine to give the appropriate amidines.

Reaction Scheme



3 **2** **1**

NHR_1R_2= 1a) methylpiperazine,
1b) ethylpiperazine,
1c) benzylpiperazine,
1d) phenylpiperazine

Reagents and conditions: a) $SnCl_2$/HCl, ethanol, 79^0C b) K_2CO_3/Toluene, methyl, ethyl, benzyl and phenyl piperazine

EXPERIMENTAL SECTION

Preparation of 8-amino-10-methyl (substituted) coumarino [3, 4 *b*] thieno [2,3*e*] [1, 4] diazepine hydrochlorides (2)

To a 100 mL round bottom flask placed 5-methyl-2-((3-nitro-2-oxo-*2H*chromen- 4-yl) amino) thiophene-3-carbonitriles (0.01 mol) and ethanol (20 mL) and a solution of stannous chloride dihydrate (0.03) in conc. hydrochloric acid (20 mL) was added slowly with stirring at room temperature and the resultant mixture was reflux for 4-5 hours. After completion of reaction as monitored by TLC, the reaction mixture was allowed to cool to 20-25 °C. The formed solid was collected by filtration, washed with ethanol (10 mL) and then with water (10 mL), dried and crystallized from ethanol to afford the desired product.

Preparation of 10-methyl-8-((substituted) amino) chromeno [3, 4-*b*] thieno [2, 3-*e*] [1, 4] diazepin-6(12*H*)-ones (3)

To a 50 mL round bottom flask placed 8-amino-10-methylchromeno[3,4- *b*]thieno[2,3-*e*][1,4]diazepin-6(12*H*)-one hydrochlorides (0.01 mol) and it was reflux in a mixture of appropriate secondary amine (9 mL), potassium carbonate (2.0 mol) and toluene (15 mL) for 6 to 8 hours. After completion of reaction as monitored by TLC, the reaction mixture was allowed to cool and the solvent evaporated under reduce pressure at 80°C. The residue was poured on to ice-water to formed solid, it was collected by filtration, washed with water (10 mL), dried and crystallized from ethyl acetate to afford the desired products.

Preparation of 4, 10-dimethyl-8-(4-methylpiperazin-1-yl) chromeno [3, 4-*b*] thieno [2, 3 *e*] [1, 4] diazepin-6(12*H*)-one (3a)

Yield: 65%; IR (cm^{-1}): 3235 (-N-H stretching of secondary amine), 3034 (-C-H stretching of aromatic ring), 2954 (-C-H asymmetrical stretching of CH_3 group), 2849(-C-H symmetrical stretching of CH_3 group), 1681 (-C=O stretching of coumarin ring), 1624, 1573, 1539, 1500 (-C=C stretching of aromatic ring), 1368 (-C-H asymmetrical deformation of -CH_3 group), 1312 (-C-H symmetrical deformation of CH_3 group), 1252 (-C-N vibration of amine), 1069 (-C-O-C stretching of coumarin ring); MS: *m/z* 394;

Preparation of 8-(4-ethylpiperazin-1-yl)-4, 10-dimethylchromeno [3, 4-b] thieno [2, 3-e][1,4]diazepin- 6(12H)-one (3b)

Yield: 52%; IR (cm^{-1}): 3252 (-N-H stretching of secondary amine), 3031 (-C-H stretching of aromatic ring), 2965 (-C-H asymmetrical stretching of CH_3 group), 2852 (-C-H symmetrical stretching of CH_3 group), 1689 (-C=O stretching of coumarin ring), 1608, 1578, 1550 and 1441 (-C=C- stretching of aromatic ring), 1382 (-C-H asymmetrical deformation of -CH_3 group), 1340(-C-H symmetrical deformation of CH_3 group), 1249 (-C-N vibration of amine), 1075 (-C-O-C stretching of coumarin ring); MS: *m/z* 408;

Preparation of 8-(4-benzylpiperazin-1-yl)-4, 10-dimethylchromeno [3, 4 *b*] thieno [2, 3*e*] [1, 4] diazepin-6(12*H*)-one (3c)
Yield: 80%; IR (cm^{-1}): 3274 (-N-H stretching of secondary amine), 3072 and 3005 (- C-H stretching of aromatic ring), 2964 (-C-H asymmetrical stretching of CH_3 group), 2878 (-C-H symmetrical stretching of CH_3 group), 1689 (-C=O stretching of coumarin ring), 1624, 1569, 1555, 1462 (-C=C- stretching of aromatic ring), 1376 (- C-H asymmetrical deformation of -CH_3 group), 1314 (-C-H symmetrical deformation of CH_3 group), 1250 (-C-N vibration of amine), 1070 (-C-O-C stretching of coumarin ring); MS: *m/z* 470;

Preparation of 8-(4-phenylpiperazin-1-yl)-4, 10-dimethylchromeno [3, 4-*b*] thieno [2,3-*e*] [1,4] diazepin-6(12*H*)-one (3d)
Yield: 70%; IR (cm^{-1}): 3319 (-N-H stretching of secondary amine), 3061 (-C-H stretching of aromatic ring), 2918 (-C-H asymmetrical stretching of CH_3 group), 2850 (-C-H symmetrical stretching of CH_3 group), 1676 (-C=O stretching of coumarin ring), 1629, 1599, 1568 and 1521 (-C=C- stretching of aromatic ring), 1375 (C-H asymmetrical deformation of -CH_3 group), 1348 (-C-H symmetrical deformation of CH_3 group), 1259 (-C-N vibration of amine), 1076 (-C-O-C stretching of coumarin ring); ^{1}H NMR (DMSO-d_6) δ ppm: 2.34 (s, 3H), 2.38 (s, 3H), 3.24 (s, 4H), 3.66 (s, 4H), 6.41 (s, 1H), 6.80-6.83 (t, 1H), 6.94-6.96 (d, 2H, J = 8.24 Hz), 7.14-7.18 (t, 1H), 7.21-7.25 (t, 2H), 7.27-7.29 (d, 1H, J = 7.32 Hz), 7.81-7.83 (d, 1H, J = 7.92 Hz); ^{13}C NMR δ ppm: 15.10, 15.36, 46.23, 48.54, 115.77, 116.26, 119.35 119.63, 120.43, 121.37, 121.83, 123.14, 124.84, 128.72, 130.59, 130.72, 144.63, 148.41, 150.37, 150.75, 158.62, 160.17; MS: *m/z* 456;

RESULTS AND DISCUSSION

Synthesis of substituted 10-methyl-8-((substituted) amino)chromeno[3,4-*b*]thieno[2,3-*e*][1,4]diazepin-6(12*H*)-ones from 8-amino-10-methylchromeno[3,4-*b*]thieno[2,3-*e*][1,4]diazepin-6(12*H*)-one hydrochloride. The synthesis was done by using two different 8-amino-10-methylchromeno[3,4-*b*]thieno[2,3-*e*][1,4]diazepin-6(12*H*)-one hydrochloride and different cyclic secondary amine.

7-membered rings with two heteroatom a 1, 4-diazepines having fused heterocyclic ring of coumarin and thiophene and cyclic secondary amine as a side chain. Substituted 8-amino-10-methyl chromeno[3,4-*b*]thieno[2,3-*e*][1,4]diazepin-6(12*H*)-one hydrochlorides treated with cyclic secondary amine (*N*-methyl, *N*-ethyl, *N*-phenyl and *N*-benzylpiperazine) in potassium carbonate and toluene at reflux condition to give title compounds. The products were characterized by FT-IR, mass spectra, ^{1}*H* NMR and elemental analysis.

CONCLUSION

In conclusion, the synthesis of title compounds has been done by using 3.0 mole equivalent secondary amine and potassium carbonate/toluene as solvents mixture at 100 °C. Most of the piperazinyl derivatives were easily synthesized and purified in ethyl acetate to get crystalline products.

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