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Microwave assisted synthesis of 2-hetryl amino substituted novel analogues of 1,4-benzodiazepine-5-piperidinyl carboxamides

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ABSTRACT

*The 2-iminothioethyl ether derivative of **3** underwent smooth nucleophilic displacement reaction with variety of hetryl amines and affored **4-9** in excellent yield. In this communication the importance of the incorporation of some pharmacophores such as 2-amino pyridinyl, pyrimidinyl, and benzothiazolyl in 1,4-benzodiazepine nucleus was highlighted.*

Keywords: Microwave assisted synthesis, 1,4-Bezodiazepines, 2-amino pyridine, pyrimidine and benzothiazole.

INTRODUCTION

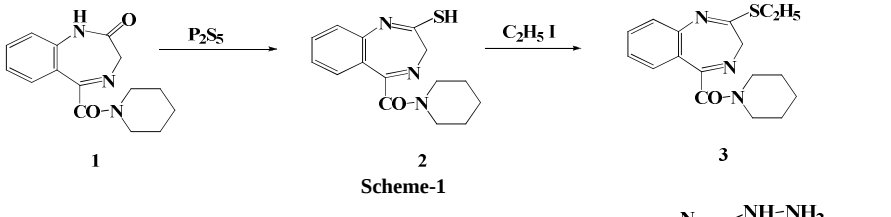
On account of the wide range of biological properties displayed by benzodiazepine derived compounds, benzodiazepine scaffolds have been considered among the most important privileged [1,2] structures for drug discovery. Particularly, 5-aryl-1,4-benzodiazepine templates are recurrent structures in anxiolytic, [3] hypnotics, [3] anticonvulsant, [4] anti-HIV activity, [5] and anti arrhythmics. [6,7] The display of different functionality upon these templates has previously provided a number of potent and specific drugs (or candidates) towards different therapeutic targets. [8]

The amide functionality (the CO-NH group) in the seven membered heterocyclic ring of 1,4-benzodiazepine nucleus is the only active functional group contained in this molecule to provide an important site for the incorporation of a wide variety of heterocycles (and fused heterocycles) and heterocycle appended structures in this molecule. This feature of the amide bearing seven membered ring has been widely exploited in many synthetic manipulations leading to enormous applications of these to be found in the literature. [9]

In the context of the current interest in methodologies for generating small bioactive molecules in laboratory, a versatile access to novel 2-amino and 5-carboxamido substituted analogues of 1,4-benzodiazepine was developed in the present work from the corresponding 5-carboxamido substituted 1,4-benzodiazepin-2-ones. The 2-chloro or 2-thiomethyl ether functionalities possessing a carbomethoxy substituent in the 1,4-benzodiazepine nucleus at 5-position was chosen to be a synthetic target for this endeavour, on this premise that their presence on the indicated position in the 1,4-benzodiazepine molecule should allow the incorporation of the amine bearing substituent on the 2-position to elicit the optimal pharmacological activity. While the synthetic access of the 2-SMe group appeared to be straight forward in contrast to the corresponding 2-chloro derivative which posed a cumbersome challenging problem in its isolation during the work up process. Therefore, 2-thiomethyl ether substituent was preferred and employed as a leaving group for its displacement by nitrogen nucleophiles. It is reported that these iminothiomethyl

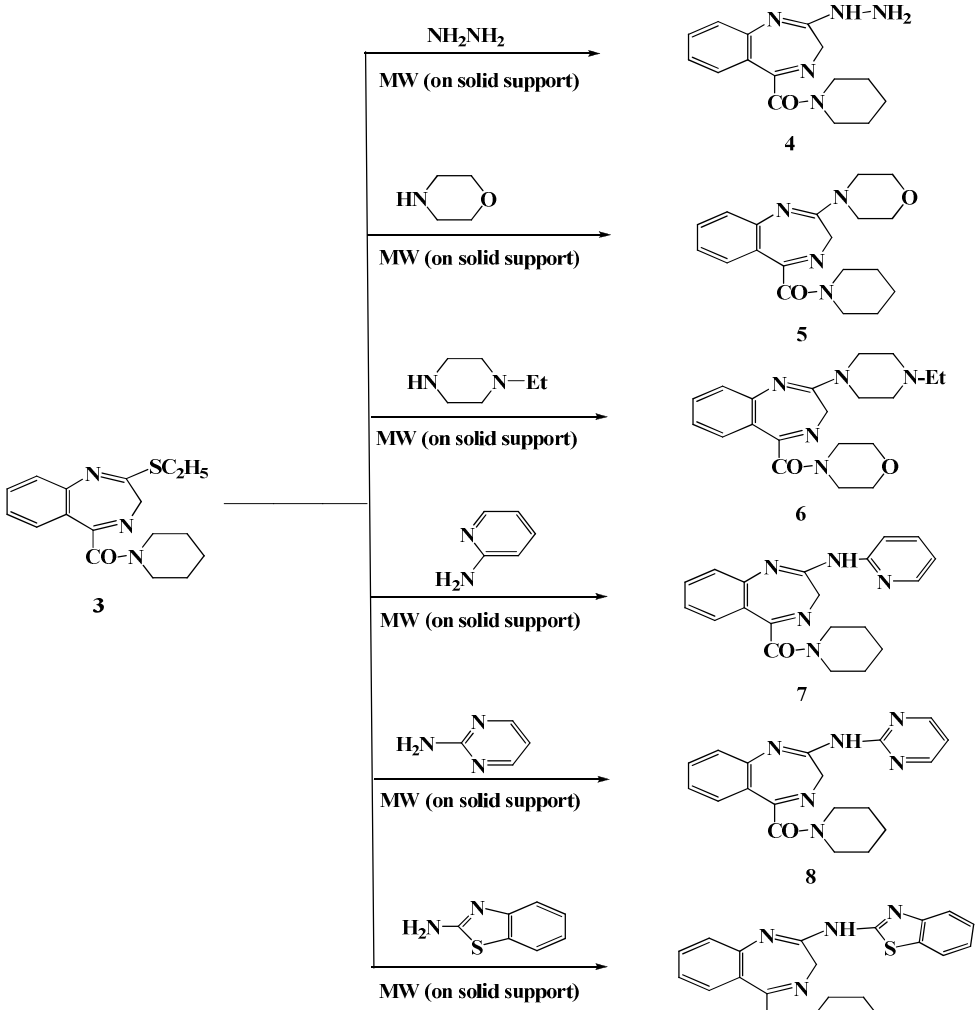
ether derivatives of 1,4-benzodiazepines are useful imidoyl derivatives known to be activated, for nucleophilic attack.

In view of the wide applicability of the microwave irradiation technique in chemical reaction rate enhancements, facilitating the reactions to take place in an environment friendly atmosphere, in a single pot, in less time, with higher yields, allowing the saving of time and energy both, we utilized this technique in the present work.



1 2 3

Scheme-1



3 4 5 6 7 8 9

Scheme-2

MATERIALS AND METHODS

Preparation of intermediate compound (2 from 1):
Solution phase microwave assisted method: Equimolar quantities of **1** (1.6 g, 0.01 mole) and Lowesson's regent (3.36 g, 0.01 mole) was taken in pyridine and placed in a 100 ml borosil flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at (360 W) microwave power for 6 min to avoid the excessive evaporation of solvent. The completion of reaction was checked by TLC. The reaction mixture was then cooled and poured on crushed ice. The separated solid was filtered washed with water and recrystallized from chloroform to give **2**, 4.47 g, (yield 90.2%), m.p. 247-248°C.

Solid phase microwave assisted method: A slurry of equimolar quantities of compound (**1**) (0.6 g, 0.01 mole), Lowesson's regent (3.36 g, 0.01 mole) and pyridine (30 ml). The dried slurry was powdered and the free flowing powder was placed in a 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethanol. The solvent was evaporated and the solid obtained was recrystallized from chloroform and dried to give **2**, 3.57 g (yield 90.2%), m.p. 247-248°C.

Preparation of intermediate compound (3 from 2):
Solution phase microwave assisted method: Equimolar quantities of **2** (3.52 g, 0.01 mole) and 1N sodium hydroxide solution (3.3 ml) followed by the slow addition of ethyliodide (4.65 g) was taken in ethanol (30 ml) and placed in a 100 ml borosil flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at (360 W) microwave power for 6 min to avoid the excessive evaporation of solvent. The completion of reaction was checked by TLC. The solution obtained after the completion of the reaction was evaporated to volume 10 ml water was added and the product was obtained by extraction with methylene chloride resulting solid obtained by evaporation and recrystallized from ethanol-hexane mixture to give **3**, 3.23 g (yield 90.0%), m.p. 185-186°C.

Solid phase microwave assisted method: A slurry of equimolar quantities of compound (**2**) (3.52 g, 0.01 mole) and 1N sodium hydroxide solution (3.3 ml) followed by the slow addition of ethyliodide (4.65 g) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (3 ml). The dried slurry was powdered and the free flowing powder was placed in a 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethanol. The solvent was evaporated and the solid obtained was recrystallized from ethanol-hexane mixture and dried to give **3**, 3.23 g (yield 90.0%), m.p. 185-186°C.

General Solution and Solid phase microwave assisted method for the preparation of (4-9) from (3).
Solution phase microwave assisted method: Equimolar quantities of **3** (0.204 g, 0.001 mole) and hydrazine hydrate (0.15 ml)/morpholine (0.087 g, 0.001 mole) and 37% formaldehyde (0.5 ml)/N-ethylpiperazine (0.1 g, 0.001 mole) and 37% formaldehyde (0.5 ml)/pyridine-2-amine (0.114 g, 0.001 mole) and 37% formaldehyde (0.5 ml)/pyrimidine-2-amine (0.123 g, 0.001 mole) and 37% formaldehyde (0.5 ml)/2-aminobenzothiazol (0.403 g, 0.001 mole) and 37% formaldehyde (0.5 ml) was taken in ethanol (5 ml) and placed in a 100 ml borosil flask fitted with a funnel as a loose top. The reaction mixture was subjected to microwave irradiation at (360 W) microwave power for 6 min to avoid the excessive evaporation of solvent. The completion of reaction was checked by TLC. The solution obtained after the completion of the reaction was evaporated to volume 10ml water was added and the product was obtained by extraction with methylene chloride resulting solid obtained by evaporation and recrystallized from methanol give **4-9** respectively with yield and m.p. as following:-

2-hydrazinyl-3-4-dihydro-1,4-benzodiazepine-5-piperidinyl carboxamide (4): 0.14 g (yield 72.0%), m.p. 168-169°C. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ(ppm): 7.67-7.03 (m, 4H, ArH), 4.49 (s, 2H, CH_2), 4.01 (s, 1H, NH), 3.34 (t, 4H, CH_2), 2.01 (s, 2H, NH_2), 1.50 (m, 6H, CH_2); IR(KBr)cm^{-1}: 3340, 3260, 1640, 1580, 1506 cm^{-1}; *m/z*: 299.37 (M^+, 45%); (Found: C, 64.38; H, 6.11; N, 23.28%. Calc. for $C_{16}H_{19}N_5O$ (299.37); C, 64.63; H, 6.44; N, 23.39%)

3-4-dihydro-2-morpholinyl-1,4-benzodiazepine-5-piperidinyl carboxamide (5): 0.19 g (yield 68.1%), m.p. 145-146°C. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ(ppm): 7.80-7.50 (m, 4H, ArH), 4.50 (s, 2H, CH_2), 3.67 (t, 4H, CH_2), 3.47 (t, 4H, CH_2), 3.34 (t, 4H, CH_2), 1.50 (m, 6H, CH_2); IR(KBr)cm^{-1}: 1645, 1531, 1242, 1032 cm^{-1}; *m/z*: 354.44 (M^+, 33%); (Found: C, 68.36; H, 6.93; N, 15.81%. Calc. for $C_{20}H_{24}N_4O_2$ (354.44); C, 68.16; H, 6.86; N, 21.30%)

3-4-dihydro-2-N-ethylpiperizinylamino-1,4-benzodiazepine-5-piperidinyl carboxamide (6): 0.21 g (yield 71%), m.p. 173-174°C. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ(ppm): 7.69-7.08 (m, 4H, ArH), 4.42 (s, 2H, CH_2), 3.08 (t, 4H, CH_2), 2.81 (t, 4H, CH_2), 3.34 (t, 4H, CH_2), 2.50 (q, 2H, CH_2), 1.50 (m, 6H, CH_2), 1.20 (t, 3H, CH_3); IR(KBr)cm^{-1}: 1655, 1515, 1233 cm^{-1}; *m/z*: 381.51 (M^+, 42%); (Found: C, 55.46; H, 9.94; N, 27.25%. Calc. for $C_{12}H_{28}N_5O$ (381.51); C, 55.78; H, 10.92; N, 27.10%)

3-4-dihydro-2-(2-piperidinylamino)-1,4-benzodiazepine-5-piperidin-1-yl carboxamide (7): 0.219 g (yield 69%), m.p. 169-170°C. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ(ppm): 8.20 (s, 1H, NH), 8.11-7.65 (m, 4H, py-H), 7.62-7.05 (m, 4H, Ar-H), 4.48 (s, 2H, CH_2), 3.47 (t, 4H, CH_2), 1.50 (m, 6H, CH_2); IR(KBr)cm^{-1}: 3265, 1650, 1502 cm^{-1}; *m/z*: 361.44 (M^+, 39%); (Found: C, 70,01; H, 5.73; N, 18.36%. Calc. for $C_{21}H_{20}N_5O$ (361.44); C, 70.37; H, 5.62; N, 19.54%)

3-4-dihydro-2-(2-pyrimidylamino)-1,4-benzodiazepine-5-piperidin-1-yl carboxamide (8): 0.22 g (yield 70%), m.p. 173-174°C. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ(ppm): 8.50 (s, 1H, NH), 8.22-8.01 (m, 3H, pyrm-H), 7.69-7.06 (m, 4H, ArH), 4.49 (s, 2H, CH_2), 3.47 (t, 4H, CH_2), 1.50 (m, 6H, CH_2); IR(KBr)cm^{-1}: 3338, 1645, 1535 cm^{-1}; *m/z*: 362.42 (M^+, 50%); (Found: C, 66.52; H, 5.39; N, 23.19%. Calc. for $C_{20}H_{20}N_6O$ (362.42); C, 66.65; H, 5.59; N, 23.32%)

3-4-dihydro-2-(2-benzothiazolyl-amino)-1,4-benzodiazepine-5-piperidin-1-yl carboxamide (9): 0.424 g (yield 71%), m.p. 169-170°C. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ(ppm): 8.20 (s, 1H, NH), 7.82-7.08 (m, 8H, ArH), 4.47 (s, 2H, CH_2), 3.47 (t, 4H, CH_2), 1.50 (m, 6H, CH_2); IR(KBr)cm^{-1}: 3340, 1640, 1530 cm^{-1}; *m/z*: 403.5 (M^+, 35%); (Found: C, 65.34; H, 5.34; N, 17.36; S, 7.85%. Calc. for $C_{22}H_{21}N_5OS$ (403.5); C, 65.49; H, 5.25; N, 23.42; S, 7.95%)

Solid phase microwave assisted method: A slurry of equimolar quantities of compound (**3**) (0.204 g, 0.01 mole), 37% formaldehyde (0.5 ml) and hydrazine hydrate (0.15 ml, 0.001 mole)/morpholine (0.087 g, 0.001 mole)/N-ethylpiperazine (0.1 g, 0.001 mole)/pyridine-2-amine (0.114 g, 0.001 mole)/pyrimidine-2-amine (0.123 g, 0.001 mole)/2-aminobenzothiazol (0.403 g, 0.001 mole) was adsorbed over basic alumina (2.0 g) via a solution in ethanol (3 ml). The dried slurry was powdered and the free flowing powder was placed in 100 ml borosil beaker and irradiated at (360 W) microwave power for 5 min and then at 720 W for 2 min until the completion of the reaction (monitored by TLC). The recyclable inorganic solid support was separated by extracting the product with ethanol. The solvent was evaporated and the solid obtained was recrystallized from ethanol-hexane mixture and dried to give **4-9** respectively, whose spectral elucidation is same as in case of solution phase synthesis, with yield and m.p. as following:-

2-hydrazinyl-3-4-dihydro-1,4-benzodiazepine-5-piperidinyl carboxamide (4): 0.42 g, (yield 93.2%), m.p. 168-169°C.

3-4-dihydro-2-morpholinyl-1,4-benzodiazepine-5-piperidinyl carboxamide (5): 0.19 g, (yield 91.6%), m.p. 170-171°C.

3-4-dihydro-2-N-ethylpiperizinylamino-1,4-benzodiazepine-5-piperidinyl carboxamide (6): 0.27 g, (yield 90.0%), m.p. 173-174°C.

3-4-dihydro-2-(2-piperidinylamino)-1,4-benzodiazepine-5-piperidin-1-yl carboxamide (7): 0.29 g, (yield 91.0%), m.p. 169-170°C.

3-4-dihydro-2-(2-pyrimidylamino)-1,4-benzodiazepine-5-piperidin-1-yl carboxamide (8): 0.29 g, (yield 91.0%), m.p. 173-174°C.

3-4-dihydro-2-(2-benzothiazolyl-amino)-1,4-benzodiazepine-5-piperidin-1-yl carboxamide (9): 0.546 g, (yield 90.0%), m.p. 169-170°C.

RESULTS AND DISCUSSION

In view of the impressive biological activities shown by the hetrylamine substituted derivatives of the 1,4-benzodiazepines, it was thought of interest in the present work to synthesize molecules which carried the hetrylamine bearing substituents at C_2 of the 1,4-benzodiazepine nucleus. The idea behind developing such a system was to incorporate in the 1,4-benzodiazepine nucleus, the biological potency of the pharmacophoric groups carrying the amine fragments, derived from the heterocyclic scaffolds which have the proven record of biological activity in the literature. [10] There is an ample record to show that libraries of several biologically active molecules have been developed through the incorporation of such bioactive pharmacophores [11] as piperazine, [12,13] morpholine, [13] piperidine, [13] amino derivatives of pyridine, [13] pyrimidine [13] and other heterocyclic amines such as 2-amino benzothiazole [14] etc**.** This prompted us to explore the possibilities of their incorporation in the 1,4-benzodiazepin-2-one nucleus. The reactivity of the 2-Cl atom and 2-SEt group in the nucleophlilic displacement reactions had made it clear that these were the two options which were open for the functionalization at C_2 position, to allow their subsequent replacement by the above mentioned pharmacophores bearing the amine fragments. Due to the obvious reasons pointed out in the introduction section, we preferred to use the corresponding SEt group (the imino thioethyl ether group) for its subsequent replacement with the indicated amines. [15]

The strategy outlined in **scheme-1** envisaged the preparation of **2** to take place from **1** from its reaction with Lowesson's reagent. Lowesson's reagent was found to give better result in the conversion of the corresponding OH to SH group than the traditional reaction with P_2S_5 reagent, therefore former was employed in the present work. Subsequent reaction of **2** with C_2H_5I afforded **3** in good yield. All the reactions outlined in **schemes-1 and 2** were carried out under the MW conditions. The MW reactions were conducted in the solution phase as well as in the solid phase (using the basic alumina as a solid support) wherein the solid phase synthesis scored better over the solution phase synthesis in giving the much higher yields of products.

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