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Synthesis of Novel Pyrimido Oxazine and their Derivatives

Sirsat Shivraj B*, Jadhav Anilkumar G, Kale Prashant S and Jadhav Madhav S

P.G. Research Centre, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded, India

***Corresponding author:** Sirsat Shivraj B, P.G. Research Centre, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded, India, Tel: 02462254487; E-mail: sbs.igm@gmail.com

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Abstract

In present report novel oxazine were prepared from starting materials chalcone and urea (1). The resulting compound 6-(4-chlorophenyl)-4-phenyl-6H-1,3-Oxazin-2-amine(2) was further reacted with ethyl 2-cyano-3,3-bis (methylthio) acrylate in the presence of catalytic amount of potassium carbonate in DMF under reflux condition that offered novel 2-(4-chlorophenyl)-8-(methylthio)-6-oxo-4-phenyl-4,6,9,9 a-tetrahydropyrimido[2,1-b][1,3]oxazine-7-carbonitrile (3). The synthesized compounds were characterized by spectral methods. The compound (3) possesses replaceable methylthio (-SCH_3) group at 8 position. The compound (3) react with various nucleophiles like substituted aromatic amines, aromatic phenols, hetryl amines and active methylene compounds to give 2-(4-chlorophenyl)-8-(substituted)-6-oxo-4-phenyl-4,6,9,9a-tetrahydropyrimido[2,1-b][1,3] oxazine-7-carbonitrile in good yields.

Keywords: Claisen-Schmidt condensation; Michael addition reaction; 2-Cyano-3, 3-bis (methylthio) acrylate; Urea

Introduction

Synthesis of compounds containing nitrogen from readily available starting materials in a cost and time effective manner has received significant and oxygen in a ring is of growing importance by virtue of their presence in numerous biologically important compounds [1-4].

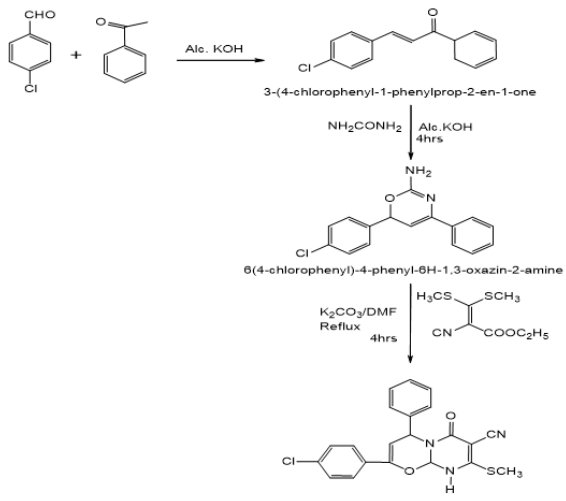

Figure 1: 2-(4-chlorophenyl)-8-(methylthio)-6-oxo-4-phenyl-4, 6, 9, 9 a tetrahydropyrimido-[2, 1-b][1,3] oxazine-7-carbonitrile.

Therefore, the development of the design and synthesis of new diverse polycyclic heterocycles with potential, Medicinal and biological activity from readily available starting materials in a cost and time effective manner has received significant attention for research in organic, combinatorial and medicinal chemistry [5-11] (Figure 1).

Oxazine and their derivatives are heterocyclic compounds containing one nitrogen and one oxygen [12]. Oxazine heterocycles have special interest because they constitute an important class of natural and non-natural products and show useful biological activities [13]. The 1, 4-oxazine scaffold is a structural subunit of many naturally occurring and synthetic bioactive compounds and have diverse biological activities such as antiulcer [14], antihypertensive [15], antifungal [16], anticancer [17] and anti-thrombotic compound [18]. In the view of this observation and extension of earlier work, we have synthesized 2-(4-chlorophenyl)-8-(methylthio)-6-oxo-4-chlorophenyl-4,6,9,9a-tetrahydropyrimido[2,1-b] [1,3]oxazine-7carbonitrile by using 6-(4-chlorophenyl)-4-phenyl-6H-1,3-Oxazin-2-amine [13,19] and 3-(4-chlorophenyl)-1-phenyl prop-2en-1-one (chalcone) [20,21].

Materials and Methods

Melting points were determined in open capillary tubes and are uncorrected. The silica gel F_{254} plates were used for thin layer chromatography (TLC); the spots were examined under UV light and then developed in an iodine vapor. Column chromatography was performed with silica gel (BDH 100-200 mesh). Solvents were purified according to standard procedures. The spectra were recorded as follows: IR, KBr pellets, a Perkin-Elmer RX1 FT-IR spectrophotometer; ^1H NMR, $CDCl_3$, 200 MHz, a Varian Gemini 200 instrument. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

Methods of preparation of compound (3)

2-(4-chlorophenyl)-8-(methylthio)-6-oxo-4-phenyl-4, 6, 9, 9 a tetrahydropyrimido-[2,1-b][1,3] oxazine-7-carbonitrile

Step-I: A solution of KOH 50% is added to an equimolar solution of acetophenone (0.01 moles) and 4-chlorobenzaldehyde (0.01 moles) in

ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. They are crystallized by ethanol compound.

Step-II: A mixture of chalcone i.e., 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (2.42 gm, 0.01 moles) and urea (0.60 gm, 0.01 moles) were dissolved in ethanolic potassium hydroxide solution (10 ml) was heated for 4 hrs, then it was poured into cold ice obtain 6-(4-chlorophenyl)-4-phenyl-6H-1, 3-Oxazin-2-amine (2).

Step-III: A mixture of 6-(4-chlorophenyl)-4-phenyl-6H-1, 3-Oxazin-2-amine (2) and ethyl 2-Cyano-3, 3-bis (methylthio) acrylate in the presence of catalytic amount of potassium carbonate (10 mg) in DMF was refluxed for 4 hrs the reaction was monitored by TLC. After complete ion, the reaction mixture was cooled at room temperature then wash with water the extracted with ethyl acetate. The extract was concentrated and the residue was subjected to column chromatography (silicagel, n-hexane-ethyl acetate 8: 2) to obtain pure solid compound 2-(4-chlorophenyl)-8-(methylthio)-6-oxo-4-phenyl-4, 6, 9, 9 a-tetrahydropyrimido[2,1-b][1, 3] oxazine-7-car-bonitrile (3). The compound (3) confirmed by IR, 1H, C_{13} NMR and MS analytical data

2-(4-chlorophenyl)-8-(methylthio)-6-oxo-4-phenyl-4, 6, 9, 9 a-tetrahydro-pyrimido [2, 1-b][1, 3] oxazine-7-carbonitrile (3)

IR: (cm^{-1}) 3330, 2210, 1650, 748; **^{1}H NMR**: (δ) 2.41 (s, 3H, SCH_3), 5.10 (s, 1H N-H), 5.50 (s, 1H =CH), 6.62 (s, 1H CH), 5.48 (s, 1H CH), 7.10(s, 5H Ar-H), 7.18(dd, 2H Ar-H), 7.25 (dd, 2H Ar-H), **ESI-MS:** m/z (M^+) 409 (M+2) 411. **Anal. Calcd for** $C_{21}H_{16}ClN_3O_2S$: C, 61.53; H, 3.93; Cl, 8.65; N, 10.25; O, 7.81; S, 7.83; **Found:** C, 61.43; H, 3.95; Cl, 8.60; N, 10.35; O, 7.82; S, 7.85. **Mol. Formula:** $C_{21}H_{16}ClN_3O_2S$. Mol. Wt: 409.

Methods of preparation of derivatives (3A-6B)

A mixture of (3) (1 mmol) and independently, various substituted aromatic amines, aromatic phenols, heteryl amines and active methylene compounds (1 mmol) in DMF (10 ml) and anhydrous potassium carbonate (10 mg) was reflux for 4 to 6 hrs. The reaction mixture cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystallized using ethyl alcohol.

2-(4-chlorophenyl)-6-oxo-8-phenoxy-4-phenyl-4, 6, 9, 9 a-tetrahydropyrimido-[2, 1-b][1, 3]oxazine-7-carbonitrile (3a)

IR: (cm^{-1}) 3330, 2210, 1650, 748; **^{1}H NMR:** (δ) 6.99 (s, 5H, Ar-H), 5.12 (s, 1H N-H), 5.50 (s, 1H =CH), 6.61 (s, 1H CH), 5.46 (s, 1H CH), 7.14 (s, 5H Ar-H), 7.22 (dd, 2H Ar-H), 7.36 (dd, 2H Ar-H) ESI-MS: m/z (M^+)455 (M+2) 457. **Anal. Calcd for** $C_{26}H_{18}ClN_3O_3$: C, 68.50; H, 3.98; Cl, 7.78; N, 9.22; O, 10.52; **Found:** C, 68.48; H, 3.97; Cl, 7.77; N, 9.21; O, 10.49. **Mol. Formula:** $C_{26}H_{18}ClN_3O_3$. **Mol. Wt:** 455.

8-(4-bromophenoxy)-2-(4-chlorophenyl)-6-oxo-4-phenyl-4, 6, 9, 9 a-tetra hydropyrimido[2, 1-b][1, 3]oxazine-7-carbonitril (3b)

IR: (cm^{-1}) 3330, 2210, 1650, 748, 650; **^{1}H NMR**: 5.11 (s, 1H N-H), 5.50 (s, 1H=CH), 6.71 (s, 1H CH), 5.51 (s, 1H CH), 7.20 (s, 5H Ar-H), 7.30 (dd, 2H Ar-H), 7.42 (dd, 2H Ar-H), 6.68 (dd, 2H Ar-H), 7.32 (dd 2H Ar-H) ESI-MS: m/z (M+) 533(M+2) 535. **Anal. Calcd for** $C_{26}H_{17}BrClN_3O_3$ C, 58.39; H, 3.20; Br, 14.94; Cl, 6.63; N, 7.86; O, 8.98. **Found:** C, 58.35; H, 3.24; Br, 14.92; Cl, 6.65; N, 7.88; O, 8.96 Mol. **Formula:** $C_{26}H_{17}BrClN_3O_3$. Mol. Wt: 534.

2-(4-chlorophenyl)-8-(4-nitrophenoxy)-6-oxo-4-phenyl-4, 6, 9, 9 a-tetra-hydropyrimido [2, 1-b][1,3]oxazine-7-carbonitrile (3c)

IR: (cm^{-1}) 3330, 2210, 1650, 748, 1510. **^{1}H NMR** : 5.13(s, 1H N-H), 5.53(s, 1H=CH), 6.69 (s, 1H CH), 5.52(s, 1H CH), 7.22(s, 5H Ar-H), 7.32(dd, 2H Ar-H), 7.20(dd, 2H Ar-H), 7.18(dd 2H Ar-H), 8.05(dd 2H Ar-H) **ESI-MS:** m/z (M^+) 500 (M+2) 502. **Anal. Calcd for** $C_{26}H_{17}ClN_4O_5$: C, 62.34; H, 3.42; Cl, 7.08; N, 11.19; O, 15.97. **Found:** C, 62.32; H, 3.38; Cl, 7.12; N, 11.18; O, 16.00. **Mol. Formula:** $C_{26}H_{17}ClN_4O_5$. **Mol. Wt:** 500.

2-(4-chlorophenyl)-6-oxo-4-phenyl-8-(phenylamino)-4, 6, 9, 9 a tetrahydropyrimido [2, 1-b][1, 3]oxazine-7-carbonitrile (4a)

IR: (cm^{-1}) 3330, 2210, 1650, 748, 3250; ^{1}H NMR : 5.09 (s, 1H N-H), 4.15 (s 1H N-H), 5.52 (s, 1H =CH), 6.71 (s, 1H CH), 5.50 (s, 1H CH), 7.22 (s, 5H Ar-H), 7.29 (dd, 2H Ar-H), 7.36 (dd, 2H Ar-H), 7.02 (s 5H Ar-H). ESI-MS: m/z (M+) 454 (M+2) 456. **Anal. Calcd for** $C_{26}H_{19}ClN_4O_2$: C, 68.65; H, 4.21; Cl, 7.79; N, 12.32; O, 7.03. **Found:** C, 68.68; H, 4.19; Cl, 7.78; N, 12.33; O, 7.02. **Mol. Formula:** $C_{26}H_{19}ClN_4O_2$. **Mol. Wt:** 454.

8-((4-bromophenyl)amino)-2-(4-chlorophenyl)-6-oxo-4-phenyl-4, 6, 9, 9 a tetrahydro-pyri mido[2,1-b][1, 3]oxazine-7-carbonitrile (4b)

IR: (cm^{-1}) 3330, 2210, 1650, 3250, 640, 748; **^{1}H NMR:** 5.13 (s, 1H N-H), 4.13 (s 1H N-H), 5.41(s, 1H=CH), 6.69 (s, 1H CH), 5.52 (s, 1H CH), 7.20(s, 5H Ar-H), 7.31 (dd, 2H Ar-H), 7.34 (dd, 2H Ar-H), 6.50 (dd 2H Ar-H), 7.16 (dd 2H Ar-H). ESI-MS: m/z (M^+) 532 (M+2) 534. **Anal. Calcd for** $C_{26}H_{18}BrClN_4O_2$: C, 58.50; H, 3.40; Br, 14.97; Cl, 6.64; N, 10.50; O, 5.99. **Found:** C, 58.48; H, 3.48; Br, 14.96; Cl, 6.60; N, 10.47; O, 6.01. **Mol. Formula:** $C_{26}H_{18}BrClN_4O_2$. **Mol. Wt:** 532.

2-(4-chlorophenyl)-8-((4-nitrophenyl)amino)-6-oxo-4-phenyl-4, 6, 9, 9 a tetrahydro-pyrim ido[2, 1-b][1, 3]oxazine-7-carbonitrile (4c)

IR: (cm^{-1}) 3330, 2210, 1650, 3250, 1480, 748. **^{1}H NMR** : 5.11 (s, 1H N-H), 4.0 (s 1H N-H), 5.43 (s, 1H=CH), 6.67(s, 1H CH), 5.48 (s, 1H CH), 7.12 (s, 5H Ar-H), 7.29 (dd, 2H Ar-H), 7.27 (dd, 2H Ar-H), 6.66 (dd 2H Ar-H), 7.95 (dd 2H Ar-H). ESI-MS: m/z (M^+) 499 (M+2) 501. **Anal. Calcd for** $C_{26}H_{18}ClN_5O_4$: C, 62.93; H, 3.72; Cl, 7.14; N, 12.23; O, 8.60. **Found:** C, 62.60; H, 3.70; Cl, 9.08; N, 14.22; O, 10.49. **Mol. Formula:** $C_{26}H_{18}ClN_5O_4$. **Mol. Wt:** 499.

2-(4-chlorophenyl)-6-oxo-4-phenyl-8-(pyrrolidin-1-yl)-4,6,9,9a-tetrahydro pyrimido[2, 1-b][1, 3]oxazine-7-carbonitrile (5a)

IR: (cm^{-1}) 3330, 2210, 1650, 748; **^{1}H NMR**: 5.13 (s, 1H N-H), 5.54 (s, 1H =CH) 6.72 (s, 1H CH), 5.52 (s, 1H CH), 7.13 (s, 5H Ar-H), 7.30 (dd, 2H Ar-H), 7.39 (dd, 2H Ar-H), 2.6 (t 4H), 1.65 (m 4H). **ESI-MS:** m/z (M^+) 432 (M+2) 434. **Anal. Calcd for** $C_{24}H_{21}ClN_4O_2$: C, 66.59; H, 4.89; Cl, 8.19; N, 12.94; O, 7.39. **Found:** C, 66.45; H, 4.61; Cl, 8.55; N, 12.78; O, 7.33. **Mol. Formula:** $C_{24}H_{21}ClN_4O_2$. **Mol. Wt:** 432.

2-(4-chlorophenyl)-6-oxo-4-phenyl-8-(piperidin-1-yl)-4,6,9,9 a-tetrahydro pyrimido[2, 1-b][1, 3]oxazine-7-carbonitrile (5b)

IR: (cm^{-1}) 3330, 2210, 1650, 748; **^{1}H NMR:** 5.12 (s, 1H N-H), 5.51 (s, 1H =CH) 6.70 (s, 1H CH), 5.49 (s, 1H CH), 7.17 (s, 5H Ar-H), 7.32 (dd, 2H Ar-H), 7.41 (dd, 2H Ar-H), 3.12 (t 4H), 1.56 (m 6H). **ESI-MS:** m/z (M^+) 446 (M+2) 448. **Anal. Calcd for** $C_{25}H_{23}ClN_4O_2$: C, 67.18; H, 5.19; Cl, 7.93; N, 12.54; O, 7.16. **Found:** C, 67.18; H, 5.25; Cl, 7.94; N, 12.52; O, 7.11. **Mol. Formula:** $C_{25}H_{23}ClN_4O_2$. **Mol. Wt:** 446.

2-(2-(4-chlorophenyl)-7-cyano-6-oxo-4-phenyl-4,6, 9, 9 a-tetrahydroPyrimido-[2, 1-b][1, 3]oxazin-8-yl) malononitrle. (6a)

IR: (cm^{-1}) 3330, 2210, 1650, 2950, 748; **^{1}H NMR**: 5.13 (s, 1H N-H), 5.52 (s, 1H=CH) 6.71 (s, 1H CH), 5.53 (s, 1H CH), 7.21(s, 5H Ar-H), 7.30 (dd, 2H Ar-H), 7.41 (dd, 2H Ar-H), 4.14 (s, 1H act-CH). **ESI-MS:** m/z (M^+) 427 (M+2) 429. **Anal. Calcd** for $C_{23}H_{14}ClN_5O_2$: C, 64.57; H, 3.30; Cl, 8.29; N, 16.37; O, 7.48. **Found:** C, 64.62; H, 3.28; Cl, 8.27; N, 16.34; O, 7.49. **Mol. Formula:** C23H14ClN5O2. **Mol. Wt**: 427.

ethyl2-(2-(4-chlorophenyl)-7-cyano-6-oxo-4-phenyl-4,6,9,9 a-tetrahydroPyrimido[2, 1-b][1, 3]oxazin-8-yl)-2-cyanoacetate. (6b)

IR: (cm^{-1}) 3330, 2210, 1650, 1950, 1710, 748; **^{1}H NMR**: 5.10 (s, 1H NH), 5.53 (s, 1H =CH), 6.68 (s, 1H CH), 5.49 (s, 1H CH), 7.18 (s, 5H Ar-H), 7.27 (dd, 2H Ar-H), 7.38 (dd, 2H Ar-H), 3.95 (s 1H act-CH), 4.18 (q 2H), 1.19 (t 3H). **ESI-MS:** m/z (M^+) 474 (M+2) 476. **Anal. Calcd for** $C_{25}H_{19}ClN_4O_4$: C, 64.80; H, 3.85; Cl, 7.97; N, 12.59; O, 10.79. **Found:** C, 64.82; H, 3.83; Cl, 7.96; N, 12.57; O, 10.82. **Mol. Formula:** $C_{25}H_{19}ClN_4O_4$. **Mol. Wt:** 474 (Figure 2).

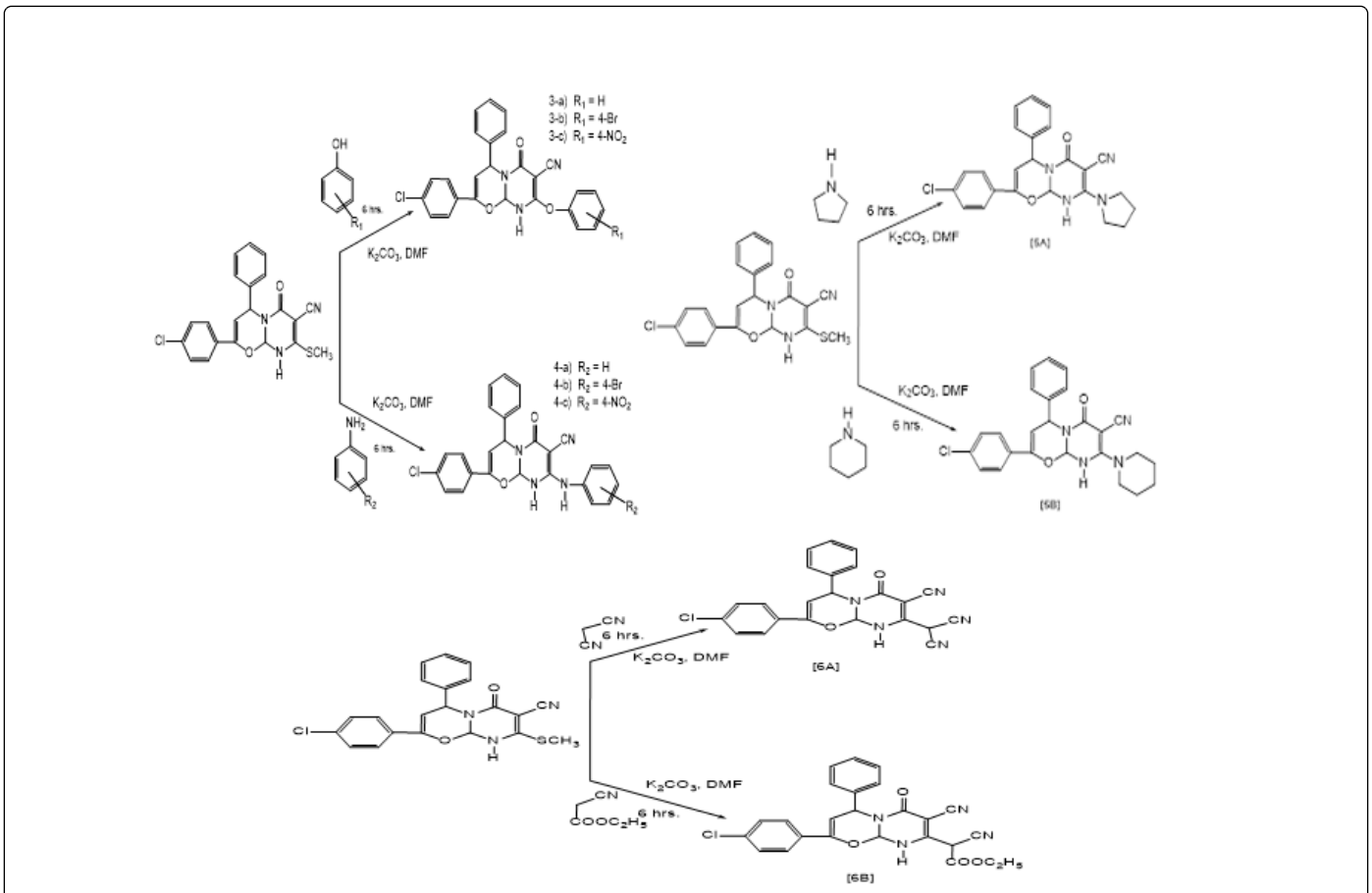

Figure 2: 2-(4-chlorophenyl)-8-(substituted)-6-oxo-4-phenyl-4, 6, 9, 9a-tetrahydropyrimido [2, 1-b] [1,3] oxazine-7-carbonitrile. (Derivatives [3A-6B]).

Discussion and Conclusion

A new different 2-(4-chlorophenyl)-8-(methylthio)-6-oxo-4-phenyl-4,6,9,9 a-tetrahydro pyrimido [2,1-b][1,3]oxazine-7-carbonitrile are synthesized by using simple and efficient chemistry and this synthesized compounds possesses methylthio group at 8-position which is best leaving group therefore synthesized compound act as an electrophilic species and reacting with various nucleophiles. In compound (3) cyano and thiomethyl groups are at adjacent position it also undergoes cyclization to give polycyclic heterocyclic compound.

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