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A facile one pot synthesis of some new 2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinolines under microwave irradiation in solvent free conditions

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A series of some new 2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinolines have been synthesized by the one pot reaction between 2-chloro-3-formylquinolines **1a–i** and thiobenzamide using *p*-TsOH catalyst under microwave irradiation. The procedure is simple, environmentally benign and occurs in good yields. All the new compounds were characterized by elemental analyses, IR, ^{1}H NMR and mass spectral data.

Keywords: 2-Chloro-3-formylquinolines; Thiobenzamide; 1,3-Thiazines; Microwave; Solvent-free

1. Introduction

Several polycyclic analogues of natural or synthetic antitumor agents are well known, and have attracted considerable interest because of their significant anticancer activity [1–4]. There is evidence that the antitumor activity is due to the intercalation between the base pairs of DNA and interference with normal functioning of the enzyme topoisomerase II which is involved in the breaking and releasing of DNA strands [5]. The intercalative binding of these drugs is due to the presence of planar linearly fused tri and tetracyclic system. Organosulfur compounds are useful materials and most of these have diverse biological applications. Recently, various fused system containing sulfur atoms such as thiophene [6, 7] benzothiazoloquinolines [8] have been studied for their intercalative property.

On the other hand condensed quinoline based heterocycles exhibit antitumor, antimicrobial, hypocholesterolemic, hypolemic antifungal and antiviral activities [9–12]. Further, 1,3-thiazines and their derivatives constitute a class of important compounds possessing diverse type of biological properties such as antibacterial [13], antitumor [14], antibiotic [15], antitubacular [16], analgesic [17], antimalarial [18] insecticidal, fungicidal activities [19–21],

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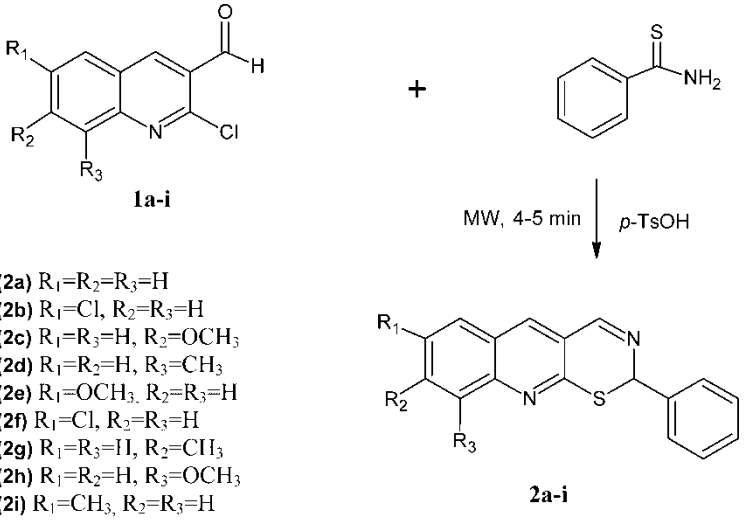
antischizophrenic effects [22], and have also reported to show antiproliferative effect in several tissue cultures [23].

Microwave-assisted heating has been shown to be an invaluable technology in synthesis since it often dramatically reduces reaction times, typically from days or hours to minutes of even seconds. And it can also provide pure products in quantitative yields. Solvent free reaction techniques were successfully coupled with microwave because they avoid the use of low boiling points and high vapor pressure solvents, which may sometimes lead to explosions. Additionally, it can also avoid the use of poisonous and expensive solvents, and as such can be environmentally benign, and make manipulations much easier. The use of microwave for the synthesis of organic compounds under solvent-free conditions proved to be efficient safe and environmentally benign techniques with shorter reaction time, high yields, and easier manipulation [24, 25]. In view of the above findings and in continuation of our work on microwave assisted synthesis of biologically important condensed heterocycles [26–29] herein we wish to report a simple, convenient microwave assisted synthesis of 2-phenyl-2*H*-[1,3]thiazino[6,5-*b*] quinolines **2a–i** from the reaction of 2-chloro-3-formyl-quinolines and thiobenzamide in the presence of *p*-TsOH catalyst in a shorter time with good yield (scheme 1).



SCHEME 1

2. Results and discussion

The starting compound 2-chloro-3-formyl quinolines, **1a–i** were prepared according to the literature method [30]. As shown in scheme 1, the reaction expected to proceed through nucleophilic substitution of chlorine at C-2 of quinoline ring by the sulfur moiety followed by the condensation of aldehyde group of quinoline and amine group of thiobenzamide in the presence of *p*-TsOH catalyst [31].

The structures of the compounds were confirmed on the basis of elemental analysis and spectral data (experimental section). As an example, the IR (KBr) spectrum of the compound **2a** showed an absence of −CHO stretching frequency at 1670 cm^{-1} which appeared in the 2-chloro-3-formylquinoline, and new absorption band appeared at 1645 cm^{-1} due to C=N group, in the newly formed ring was the evidence of the ring closure. ^{1}H NMR (DMSo-d_6)

spectrum of **2a** in addition to aromatic protons resonated between δ6.90–7.92 ppm (10 H) exhibited a singlet at δ5.2 ppm corresponding to −CH proton and singlet at δ8.15 ppm corresponds to CH=N proton indicating the attachment of the reactive partner to the quinoline substrate. Finally, the structure was confirmed by its mass spectrum through the appearance of molecular ion peak at m/z 276 [M+]. We synthesized eight more title compounds, which exhibited similar spectral characteristics (Section 4).

3. Conclusion

In conclusion, a simple efficient and environmentally benign method has been developed for the synthesis of 2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinolines under solvent free conditions in presence of *p*-TsOH. This microwave irradiation method is superior from the view of yield, reaction time and facial work up compared to the conventional (thermal) method.

4. Experimental

Melting points are determined in open capillaries and are uncorrected. The FT-IR spectra were recorded on NICOLETAVATAR 360-FTIR instrument by using KBr pellets. The ^{1}H NMR were recorded on a BRUCKER AMX-400 spectrometer operating at 400 MHz. Mass spectra were recorded on AGILENT LC-MSD-TRAP-XCT mass spectrometer Elemental analyses were done on Vario EL. CHNOS elemental analyzer.

4.1 *General MW procedure for the synthesis of substituted 2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinolines 2a-i*

Mixture of substituted quinoline **1a** (0.764 g, 0.004 mol) and thiobenzamide (0.685 g, 0.005 mol), and catalytic amount of *p*-TsOH were ground thoroughly then the contents were irradiated in a microwave oven for about 4 minutes at an interval of 1 min at 160 W. The completion of reaction was monitored by TLC, the product **2a** was poured into ice-cold water. The obtained greenish yellow colour solid was filtered washed with water then recrystallised from aqueous DMF, gave 85% yield. The same procedure was used for the synthesis of **2b–i**.

4.2 *Conventional method*

To a mixture of substituted quinoline **1a** (0.764 g, 0.004 mol) and thiobenzamide (0.685 g, 0.005 mol), and catalytic amount of *p*-TsOH and 20 ml absolute ethanol were taken in 100 ml round bottom flask, kept for reflux for about 6 hours after the completion of the reaction confirmed by TLC, reaction mixture was concentrated then poured into ice cold water. The obtained greenish yellow colour solid was filtered washed with water then recrystallised from aqueous DMF. The same procedure was used for the synthesis of **2b–i**.

4.3 *Physical and spectral data of the products*

4.3.1 2-Phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2a. Solid, m.p. 165–166 °C; Yield 85% (MW), 67% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.2 (s, 1H, H2), 6.90–7.92 (m, 10H, Ar-H), 8.15 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1645 (C=N); MS, m/z 276 [M+], Anal. Calcd for $C_{17}H_{12}N_2S$: C, 73.91; H, 4.35; N, 10.14. Found: C, 73.96; H, 4.38; N, 10.19.

4.3.2 7-Bromo-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2b. Solid, m.p. 215–217 °C; Yield 86% (MW), 68% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.25 (s, 1H, H2), 7.03–8.02 (m, 9H, Ar−H), 8.20 (s, 1H, H-3); IR (KBr) ν (cm^{-1}): 1655 (C=N); MS, m/z 355 [M+], Anal. Calcd for $C_{17}H_{11}N_2BrS$: C, 57.46; H, 3.10; N, 7.88. Found: C, 57.49; H, 3.15; N, 7.90.

4.3.3 8-Methoxy-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2c. Solid, m.p. 174–176 °C; Yield 88% (MW), 70% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.22 (s, 1H, H2), 6.95–7.94 (m, 9H, Ar−H), 8.18 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1640 (C=N); MS, m/z 306 [M+], Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.58; H, 4.57; N, 9.15. Found: C, 70.62; H, 4.59; N, 9.19.

4.3.4 9-Methyl-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2d. Solid, m.p. 181–183 °C; Yield 85% (MW), 69% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.28 (s, 1H, H2), 7.02–8.04 (m, 9H, Ar−H), 8.20 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1650 (C=N); MS, m/z 290 [M+], Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.48; H, 4.82; N, 9.95. Found: C, 74.52; H, 4.78; N, 9.9.

4.3.5 7-Methoxy-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2e. Solid, m.p. 185–187 °C; Yield 84% (MW), 68% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.22 (s, 1H, H2), 6.94–7.95 (m, 9H, Ar−H), 8.18 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1645 (C=N); MS, m/z 306 [M+], Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.58; H, 4.57; N, 9.15. Found: C, 70.60; H, 4.60; N, 9.17.

4.3.6 7-Chloro-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2f. Solid, m.p. 201–203 °C; Yield 87% (MW), 70% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.24 (s, 1H, H2), 7.03–8.03 (m, 9H, Ar−H), 8.20 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1650 (C=N); MS, m/z 310 [M+], Anal. Calcd for $C_{17}H_{11}N_2SCl$: C, 65.80; H, 3.54; N, 9.03. Found: C, 65.85; H, 3.58; N, 9.06.

4.3.7 8-Methyl-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2g. Solid, m.p. 178–180 °C; Yield 85% (MW), 68% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.24 (s, 1H, H2,), 6.93–7.96 (m, 9H, Ar−H), 8.20 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1655 (C=N); MS, m/z 290 [M+], Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.48; H, 4.82; N, 9.95. Found: C, 74.55; H, 4.75; N, 9.98.

4.3.8 9-Methoxy-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2h. Solid, m.p. 188–190 °C; Yield 86% (MW), 65% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.26 (s, 1H, H2), 7.04–8.05 (m, 9H, Ar-H), 8.18 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1640 (C=N); MS, m/z 306 [M+], Anal. Calcd for $C_{18}H_{14}N_2OS$: C, 70.58; H, 4.57; N, 9.15. Found: C, 70.64; H, 4.56; N, 9.20.

4.3.9 7-Methyl-2-phenyl-2*H*-[1,3]thiazino[6,5-*b*]quinoline 2i. Solid, m.p. 193–195 °C; Yield 88% (MW), 71% (Conventional); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 5.22 (s, 1H, H2), 7.06–8.03 (m, 9H, Ar-H), 8.18 (s, 1H, H3); IR (KBr) ν (cm^{-1}): 1645 (C=N); MS, m/z

290 [M+], Anal. Calcd for $C_{18}H_{14}N_2S$: C, 74.48; H, 4.82; N, 9.95. Found: C, 74.49; H, 4.83; N, 9.92.

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