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A microwave assisted synthesis of few 7-mercaptobenzimidazolyl fluoroquinolones

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ABSTRACT

*A series of new 7-mercaptobenzimidazolyl fluoroquinolone compounds **(3a-e)**were synthesized using microwave irradiation technique starting from (3S)-9, 10-difluoro-3-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid. The structures of the synthesized compounds were established on the basis of their spectral and analytical data and were found in good agreement with that of the compounds obtained by conventional chemical methods.*

Keywords: 7-mercaptobenzimidazolyl fluoroquinolones, microwave irradiation, triethylamine adsorbed silica gel.

INTRODUCTION

Fluoroquinolones are well established class of broad spectrum antibiotics, therapeutically useful in the treatment of various pathogenic infections due to their extensive potent activity against various microorganisms [1] [2] [3] [4] and are commonly prescribed antibiotics.Fluoroquinolones exhibit various pharmacological properties such as anti-inflammatory[5],analgesic [6], antimicrobial [7] and antiviral activities [8]. A wide variety of therapeutically interesting drugs such as Ciprofloxacin, Levofloxacin, Moxifloxacin, etc., are incorporated with fluoroquinolones moiety. Asurvey of the literature indicates that the substitution and chemical manipulation at position7 of the fluoroquinolone ring system (along with C-8) strongly affects the target preferences (DNA gyrase and/or DNA topoisomerase IV) of quinolones.The reported classical synthetic protocols for the fluoroquinolones suffer from some disadvantages like prolonged reaction time, use of hazardous chemicals, solvents, low yields and complicated work up procedures. In this connection and by knowing the importance/advantages of MORE (Microwave induced Organic Reaction Enhancement) chemistry, we felt that the synthesis of various 7-mercaptobenzimidazolyl fluoroquinolone compounds under microwave irradiation technique as an alternative methodology.

Herein we wish to report a convenient and efficient synthesis of few 7-mercaptobenzimidazolyl fluoroquinolone **(3a-e)** under microwave irradiation to improve the efficiency, the selectivity, the reaction rates, milder reaction conditions and the formation of cleaner products in high yields.

MATERIALS AND METHODS

Uncorrected melting points were determined using Thermonik Melting point Apparatus (Campbell Electronics, India) by open capillary method. TLC methods were used to monitor the reactions using aluminum sheets coated with silica gel 60 F254 (Merck) in UV chambers. IR spectra were recorded on a Perkin-Elmer-1700 spectrometer in KBr discs.Joel instrument (Joel, Japan) was used to record ^{1}HNMR and ^{13}C NMRat 300MHz in DMSO-d_6 using Chemical shifts and were measured inδunits (ppm) relative to Tetramethylsilane (TMS). Electrospray ionization mass spectra (ES-MS) were recorded on an Avarian 300 MS- spectrometer. Microwave reactions were carried out

using a MARS 240/50 instrument, model no. 907510. Solvents were of reagent grade and were purified, dried by standard procedure.

Preparation of triethylamine absorbed silica gel:
A mixture of silica gel (100 g) and triethylamine (200 ml) was stirred for 30 min at 25-30°C. The excess of triethylamine was distilled under reduced pressure below 45°C. The obtained solid was dried under reduced pressure at 55-60°C yielded 169.6 g of triethylamine adsorbed silica gel.

Preparation of (S)-10-((3S)-10-((1H-benzo-2yl)thio)-9-fluoro-3-methyl-1-7-oxo-3,5,6,7-tetrahydro-2H[1,4] oxazino[2,3,4-ij]quinoline-6-carboxylic acid(3a):
A mixture of compound **1** (2.5g,8.89 mmol), compound **2** (1.5g, 9.98 mmol) and triethylamine adsorbed on silicagel (10 mmol) was taken in a microwave vial. The vial was sealed and placed in microwave. The power setting was held at 100W for the entire experimentand the reaction was allowed to run at 100ºC for 5 min. The reaction mixture was then cooled to room temperature. The content was washed with toluene (10 ml) and the obtained crude solid after filtration wasrecrystallized from methanol to afford the compound **3a** (3.3g)

Yield: 91%; White solid; mp:216.4°C-219.3°C; IR(KBr, cm^{-1} 3395(N-H),1721(C=O),1608(C=O); ^{1}H NMR (DMSO-d_6): δ1.43 (t,3H,CH_3), 4.45-4.64(m,2H,CH), 4.97-5.04(m,1H,CH), 7.28-7.31(m,2H,Ar-H), 7.52-7.55(m,2H,Ar-H), 7.78-7.81(d,1H,Ar-H), 9.11(s,1H,olefinic), 12.5(s,1H,COOH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6):17.8 (CH_3), 54.9 (CH), 69.3(CH_2),102.8(CH), 108(C), 109.6(C), 113.8(CH), 122.3(CH), 123.5(C), 130.2(C),132.4(C), 136.2 (C), 146.7(CH), 158 (C), 165.5 (C=O, acid), 176.7 (C=O, ketone) ; Mass (ES): *m/z* 412 $[M+H]^+$; Anal. Calcd.for $C_{20}H_{16}FN_3O_4S$: C, 58.39; H, 3.43; F 4.62; N, 10.21; O, 15.56; S 7.79. Found: C, 58.35; H, 3.42; F, 4.60; N, 10.20; O 15.55; S, 7.78.

The same procedure was followed for the preparation of other compounds 3**b-e**.

(3S)-9-fluoro-10-((5-methoxy-1H-benzo[d]imidazol-2yl)thio)-3-methyl-7-oxo-3,5,6,7-tetrahydro-2H-[1,4] oxazino[2,3,4-ij]quinoline-6-carboxylic acid (3b)
Yield: 89%; pale yellow solid; mp:242.1°C - 247.8°C;IR (KBr, cm^{-1}) ; 3410(N-H),1721(C=O),1608(C=O); ^{1}H NMR (DMSO-d_6): δ1.43 (d,3H,CH_3), 3.77(s,3H,OCH_3), 4.45-4.64 (m,2H,CH_2), 4.99-5.01(m,1H,CH), 6.90-6.93(m,1H,Ar-H), 7.00-7.01(d,1H,Ar-H), 7.41-7.44 (d,1H,Ar-H), 7.77-7.80(d,1H,Ar-H), 9.11 (s,1H,olefinic) ;^{13}C NMR (DMSO-d_6): 18.27 (CH_3), 55.4(CH), 56.1(O-CH3),69.78(CH2),96.67(CH), 103(C), 107.9(C), 108.46(C), 114.3(CH), 114.98(C), 125.0(C),128.6(C), 129.7(C), 131(C), 145.74(C), 147.1(CH),149.1(C-F),157.4(CH), 165.9(C=O, acid), 176.8 (C=O,ketone) ; Mass (ES): *m/z* 442 $[M+H]^+$; Anal. Calcd. for $C_{21}H_{16}FN_3O_5S$: C, 57.14; H, 3.65; F, 4.30; N, 9.52; O, 18.12; S, 7.26. Found: C, 57.16; H, 3.63; F, 4.32; N, 9.52; O, 18.14; S, 7.27.

(S)-10-((5-amino-1H-benzo[d]imidazole-2-yl)thio)-9-fluoro-3-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino [2,3,4-ij] quinoline-6-carboxylic acid (3c)
Yield: 88%; White solid; mp:293.5°C-298.6°C;IR(KBr, $cm^{-1)}$; 3445(N-H),1724(C=O),1623(C=O); ^{1}H NMR (DMSO-d_6): δ 1.45-1.47(d,3H,CH_3), 4.46-4.70 (m,2H,CH_2), 5.0-5.02(m,1H,CH), 7.79-7.86(m,4H,Ar-H), 9.09 (s,1H, olefinic), 14.83 (s, 1H, COOH, exchangeable with D_2O);^{13}C NMR (DMSO-d_6):17.95(CH_3), 55.08(CH), 69.05(CH_2),97.8(CH),103.6(C),103.85(CH), 107.89(C),110.2(CH),115.7(CH), 122(C), 125.2(C), 127.8(C), 132.2(C),138.6(C),144.6(C),147.27(CH),160.2(C), 165.75(C=O,acid), 176.64(C=O, ketone); Mass (ES): *m/z* 427 $[M+H]^+$; Anal. Calcd. for $C_{20}H_{15}FN_4O_4S$: C, 56.33; H, 3.55; F 4.46; N, 13.14; O, 15.01; S 7.52. Found: C, 56.35; H, 3.56; F, 4.42; N, 13.10; O,15.06; S, 7.50.

(S)-9-fluoro-3-methyl-10-((5-methyl-1H-benzo[d]imidazole-2-yl)thio)-7-oxo-3,7-dihydro-2H-[1,4] oxazino [2,3,4-ij]quinolone-6-carboxylic acid(3d)
Yield: 92%; pale yellow solid; mp:241.3°C-247.8°C;IR (KBr, cm^{-1})3391(N-H),1745(C=O),1605(C=O); ^{1}H NMR (DMSO-d_6): δ 1.42 (d, 3H,CH_3), 2.48-2.50(m,3H,CH_3-Ar), 4.45-4.63 (m,2H,CH_2), 4.99-5.01(m,1H,CH), 7.07-7.15(d,1H,Ar-H), 7.33-7.44(m, 2H,Ar-H), 7.78-7.81(d,1H,Ar-H), 9.11 (s,1H,olefinic); ^{13}CNMR(DMSO-d_6): 17.8 (CH_3),22(CH3), 55.4 (CH), 69.4 (CH_2), 105.3(CH), 109.2(C), 111.4 (C),115.9(CH), 124.9(C), 125(C), 128.9(C),130.2 (C), 132 (C), 134.23(C), 145.65(C), 148.9(C), 166.6 (C=O, acid), 176.5(C=O, ketone) ; Mass (ES): *m/z* 426 $[M+H]^+$; Anal. Calcd. for $C_{21}H_{16}FN_3O_4S$: C, 59.29; H, 3.79; F, 4.47; N, 9.88; O, 15.04; S 7.54. Found: C, 59.30; H, 3.76; H, F, 4.45; N, 9.83; O, 15.04; S, 7.52.

(S)-10-(5-chloro-1H-benzo[d]imidazol-2yl)thio-9-fluoro-3-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinolone-6-carboxylic acid(3e)
Yield:92%;White solid; mp:241.4°C-246.3°C;IR (KBr, cm^{-1}) 3418(N-H),1697(C=O),1606(C=O); ^{1}H NMR (DMSO-d_6):δ 1.42(d, 3H,CH_3),4.40-4.61(m,2H,CH_2),4.98-5.00 (m,1H.CH), 7.16-7.19(d,1H,Ar-H), 7.41-

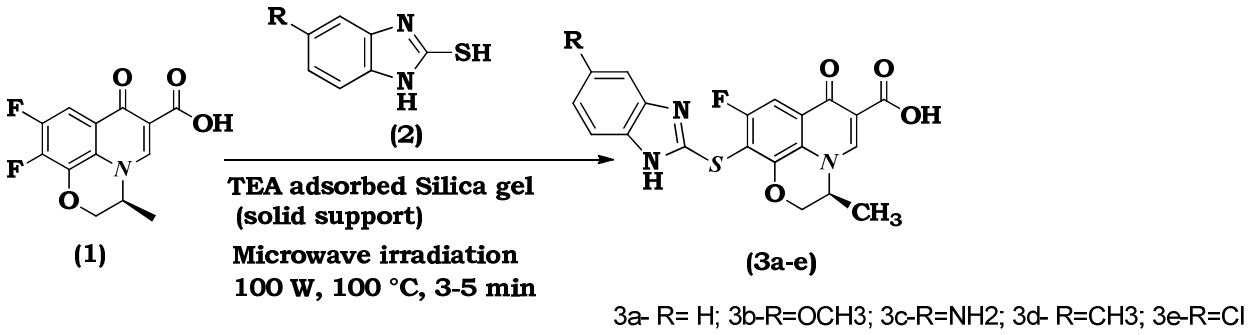
7.49(m,2H,Ar-H), 7.76-7.79(d, 1H, Ar-H),9.10(S.OlefinicH);^{13}CNMR (DMSO-d_6):17.84(CH_3), 54.96 (CH), 69.24(CH_2),98.5(CH), 107.9(C), 108.5(C), 115.1(CH),122.8(C),124.4(CH),127.8(C),130.2(C),132.4(C), 136.4(C), 138.9(C),146.7(CH), 148.3(C),149.2(C), 160.7(C),165.5(C=O, acid), 176.5(C=O, ketone) ;Mass (ES): *m/z* 446 $[M+H]^+$; Anal. Calcd. for $C_{20}H_{13}ClFN_3O_4S$: C, 53.88; H, 2.94; Cl, 7.95; F 4.26 ; N, 9.42; O, 14.35; S 7.19. Found: C, 53.86; H, 2.95; Cl, 7.93, F, 4.23; N, 9.45; O, 14.36; S, 7.20.

RESULTS AND DISCUSSION

The focus of the present investigation is on the preparation of a few (S)-10-((3S)-10-((1H-benzo-2yl)thio)-9-fluoro-3-methyl-1-7-oxo-3,5,6,7-tetrahydro-2H[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid compounds**(3a-e)** starting from compound **1**, i.e.,(3S)-9,10-difluoro-3-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acidunder microwave irradiation technique.

Initially the reaction of (3S)-9,10-difluoro-3-methyl-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid(**1)** with 2-mercapto-1*H*-benzo[d] imidazole (**2)** was carried out in various solvents like acetonitrile, DMF or DMSO by deploying bases like pyridine, triethylamine or potassium carbonate. Almost all attempts failed to give the complete conversion of starting material into the desired product with acceptable quality and quantity.

In order to make environmentally benign, an alternative synthesis of **3a-e** was carried out under microwave irradiation conditions. Thus we have achieved the synthesis avoiding the use of acetic anhydride, boric acid in solvent free conditions. This reaction was performed in presence of triethylamine adsorbed silica gel under microwave irradiation for 5 minutes at 100W (**Scheme – 1)**.



Scheme-1

Same procedure was used to prepare the other compounds **3b–e**. The structure of the compounds **3a-e** was assigned on the basis of their IR (KBr) spectrum, ^{1}H &^{13}C-NMR spectrum (DMSO-d_6) and mass spectrum.

CONCLUSION

Compounds **3a-e** were synthesized by green and environmentally benign methodology with the help of a microwave irradiation technique and the analysis of the compounds was found in good agreement with that of the compounds obtained by conventional chemical methods.The notable advantages are the experimental simplicity, shorter reaction time, high yield and easy work up.

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