

# Synthesis and Antibacterial Screening of New 4-((5-(Difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)-tetrazolo[1,5-*a*]quinoline Derivatives

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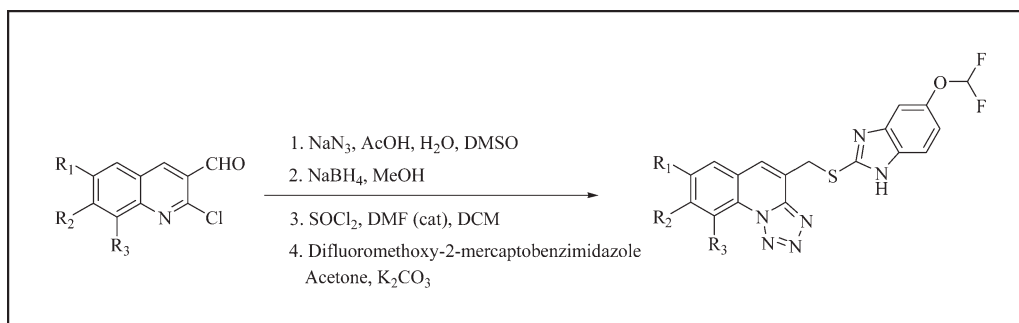
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Received July 29, 2009

DOI 10.1002/jhet.340

Published online 4 March 2010 in Wiley InterScience (www.interscience.wiley.com).



A method for the synthesis of previously unknown heterocyclic systems 4-((5-(difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-*a*]quinolines derivatives **6** has been developed based on various substitutes 2-chloroquinoline-3-carbaldehydes **1** via the consecutive steps of conversion into tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2** on treatment with sodium azide which upon reduction to the corresponding alcohol derivatives **3**, conversion to chlorides **4** with thionyl chloride followed by the coupling with 5-(difluoromethoxy)-1*H*-benzo[d]imidazole-2-thiol **5**. The synthesized titled compounds (**6a–e**) were screened for the antibacterial activity against gram positive and gram negative bacteria.

*J. Heterocyclic Chem.*, **47**, 441 (2010).

## INTRODUCTION

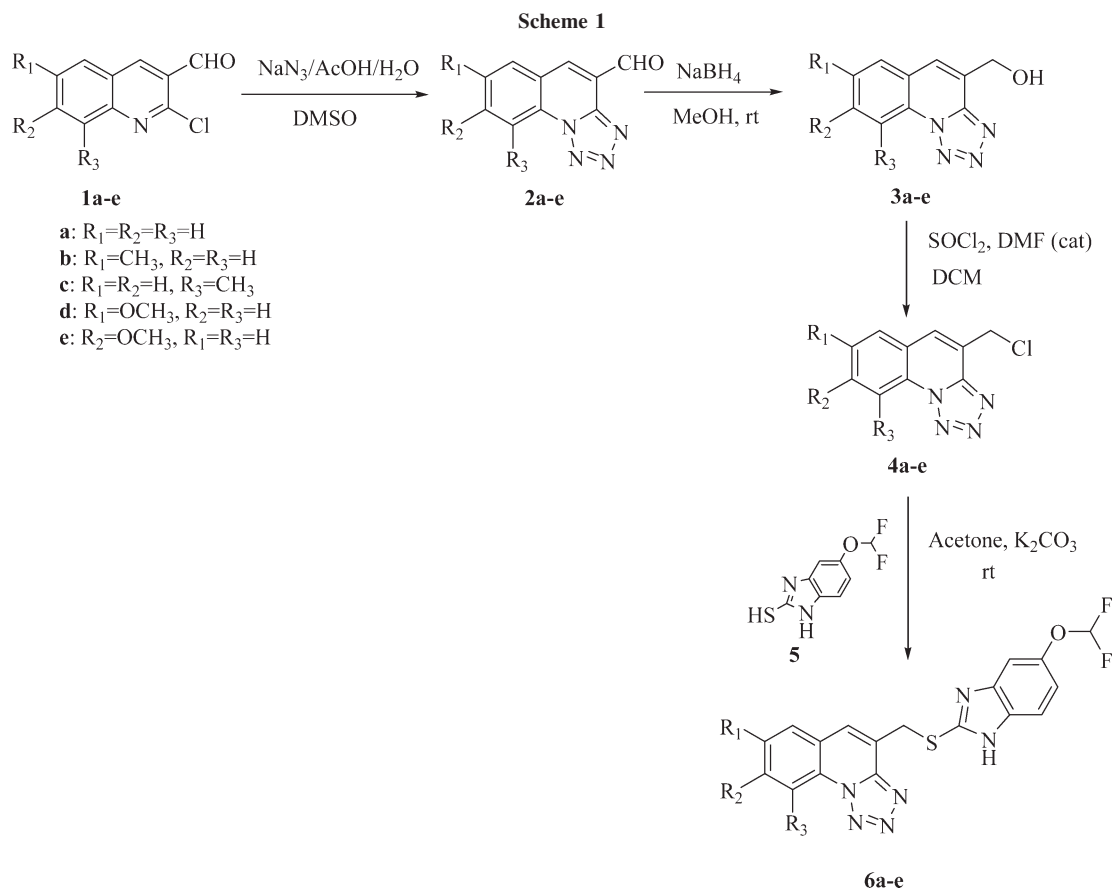
Quinoline ring systems represent a major class of heterocycles in which benzene ring is fused with pyridine ring. The derivatives of quinoline exhibit diverse biological and physiological activities such as antimalarial [1a], anti-inflammatory [1b], antitumor [1c], DNA binding capacity [1d], and antibacterial properties [1e]. Recently, quinoline has been employed in the study of bio-organic and bio-organometallic processes [1f]. The quinoline skeleton is often used as a key intermediate for the design of many pharmacologically important synthetic compounds [2].

The tetrazole group has considered analogous to carboxylic group [3] as a pharmacophore. Several substituted tetrazoles show pronounced activities such as anti-fertility [4a], CNS depressant [4b], antimicrobial [4c], anti-inflammatory [4d], and antiaids [4e]. The most prominent pharmaceutical application of tetrazoles is as angiotensin II receptor antagonists for the treatment of high-blood pressure [5]. The fusion of quinoline to the tetrazole ring is known to increase the biological activity [6]. In particular, tetrazolo[1,5-*a*]quinoline-4-carbalde-

hyde serves as a key synthetic intermediate for the synthesis of novel medicinally valuable compounds [7].

Benzimidazole scaffold has received extensive attention since the fact that it is a component of vitamin B<sub>12</sub> [8]. The derivatives of benzimidazole are possessed broad spectrum of biological activities including antibacterial, antiviral [9a], antitumor [9b], antimutagens [9c], cardiovascular [9d], anticalmodulin [9e], and many other activities are well documented [10]. In particular, mercapto benzimidazole is used for the synthesis of the most known prazole drugs pantoprazole [11a], omeprazole [11b], rabeprazole [11c], and lansoprazole [11d] which are antiulcerous agents useful in the treatment of stomach and duodenal ulcers. By all means, benzimidazole acts as “privileged substructure” for drug design [12]. Among these, pantoprazole is the proton pump inhibitor drug used in gastroesophageal reflux disease and as antihelicobacter agent [13] for the treatment of gastrointestinal disorders. Pyridine and 5-difluoromethoxy-2-mercapto-1*H*-benzimidazole are the two key constituents of this drug.

After the extensive literature search, it was observed that quinoline, tetrazole, 2-mercapto-1*H*-benzimidazole



are the important pharmacophore, but till date enough efforts have not been made to combine these three moieties as a single molecular scaffold. So, our object was to synthesize and biological screening of a series of new compounds incorporating these moieties.

## RESULTS AND DISCUSSION

In continuation of our work [14] herein, we report a simple method for the synthesis of novel 4-((5-(difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-*a*]quinolines in excellent yields (Scheme 1).

The derivatives of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **2a-e** were prepared from substituted 2-chloroquinoline-3-carbaldehyde **1a-e** on treatment with sodium azide in the presence of acetic acid. The reactions were carried out using DMSO as a solvent at 40°C. The products formed in 81–85% yields (Table 1, entries 1–5).

The synthesized tetrazolo[1,5-*a*]quinoline-4-carbaldehydes **2a-e** on reduction with sodium borohydride at room temperature stirring in methanol formed the derivatives of (tetrazolo[1,5-*a*]quinolin-4-yl)methanol **3a-e** in excellent 94–97% yields within only 10 min (Table 1, entries 6–10).

These (tetrazolo[1,5-*a*]quinolin-4-yl)methanol **3a-e** derivatives when reacted with thionyl chloride in the presence of catalytic amount of DMF formed substituted 4-(chloromethyl)tetrazolo[1,5-*a*]quinolines **4a-e**. The reactions were carried out in DCM at reflux temperature to give the products in excellent yields (97–98%) (Table 1, entries 11–15).

The reaction of 4-(chloromethyl)tetrazolo[1,5-*a*]quinoline **4a-e** with 5-(difluoromethoxy)-1*H*-benzo[d]imidazole-2-thiol **5** afforded the titled compounds 4-((5-(difluoromethoxy)-1*H*-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-*a*]quinolines **6a-e**. The mixture was stirred at room temperature in acetone. The progress of the reaction was monitored by thin layer chromatography (8:2—hexane: ethyl acetate solvent system). The reaction proceeded smoothly under basic condition (K<sub>2</sub>CO<sub>3</sub> was used as a base), and completed in 1 h to afford the corresponding titled compounds in very high yields (93–98%) (Table 1, entries 16–20). The chemical structures of all the new compounds were confirmed by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectroscopic data, and elemental analysis.

The titled compounds (**6a-e**) were screened for antibacterial activities against Gram positive *Bacillus subtilis*, *Staphylococcus aureus*, and Gram negative *Escherichia coli*, *Salmonella aboney* bacteria. The compounds

**Table 1**  
Physical data of the synthesized compounds.

Entry	Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield (%)	M.P. (°C)
1	2a	H	H	H	81	240–241
2	2b	CH <sub>3</sub>	H	H	83	230–231
3	2c	H	H	CH <sub>3</sub>	85	223–224
4	2d	OCH <sub>3</sub>	H	H	81	226–227
5	2e	H	OCH <sub>3</sub>	H	82	238–239
6	3a	H	H	H	96	189–190
7	3b	CH <sub>3</sub>	H	H	95	195–196
8	3c	H	H	CH <sub>3</sub>	94	199–200
9	3d	OCH <sub>3</sub>	H	H	96	219–220
10	3e	H	OCH <sub>3</sub>	H	97	231–232
11	4a	H	H	H	96	202–203
12	4b	CH <sub>3</sub>	H	H	97	188–189
13	4c	H	H	CH <sub>3</sub>	98	177–178
14	4d	OCH <sub>3</sub>	H	H	98	185–186
15	4e	H	OCH <sub>3</sub>	H	97	166–167
16	6a	H	H	H	93	225–226
17	6b	CH <sub>3</sub>	H	H	95	222–223
18	6c	H	H	CH <sub>3</sub>	97	227–228
19	6d	OCH <sub>3</sub>	H	H	94	205–206
20	6e	H	OCH <sub>3</sub>	H	98	195–196

tested are compared against the standard (Streptomycin) by measuring the diameter of zone of inhibition. Almost all the compounds tested exhibited moderate activity against Gram positive bacteria and a few compounds were found to be active against Gram negative bacteria used in this study (Table 2).

## EXPERIMENTAL

All the melting points were determined in open capillaries in a paraffin bath and are uncorrected. <sup>1</sup>H NMR spectra were recorded on Mercury Plus Varian in DMSO-d<sub>6</sub> at 400 MHz and Bruker DRX-300 in CDCl<sub>3</sub> at 300 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR model as KBr discs. <sup>13</sup>C NMR spectrum was recorded on Bruker DRX-300 at 75 MHz using TMS as an internal standard. Mass spectra were recorded on Micromass Quattro II using Electrospray Ionization technique. The elemental analysis was carried out on Flash EA 1112, 50/60 Hz, 1400 VA CHN analyzer. The progress of the reactions was monitored by TLC.

**General procedure.** *Tetrazolo[1,5-a]quinoline-4-carbaldehydes (2a–e).* A mixture of 2-chloroquinoline-3-carbaldehyde (10 mmol), sodium azide (1.0 g) in water (5 mL), acetic acid (2 mL), and dimethyl sulphoxide (100 mL) was stirred at 40°C for 3 h. The reaction mixture was allowed to remain at room temperature overnight. A white crystalline solid formed was filtered off, washed with water, dried, and recrystallized from acetone.

*(Tetrazolo[1,5-a]quinolin-4-yl)methanol (3a–e).* To the stirred solution of tetrazolo[1,5-a]quinoline-4-carbaldehydes (10 mmol) in 15 mL methanol was slowly added sodium borohydride (0.25 g) at room temperature. The progress of reaction was monitored on TLC (8:2—petroleum ether:ethyl acetate). After the completion of the reaction (10 min), the reaction mixture was

concentrated under reduced pressure to obtain residue. To this residue, ice cold water was added and the solid obtained was filtered off to get product 3. ES-MS: m/z 201 (m + 1).

*4-(Chloromethyl)tetrazolo[1,5-a]quinolines (4a–e).* To the stirred solution of (tetrazolo[1,5-a]quinolin-4-yl)methanol (10 mmol) in DCM (10 mL) was added dropwise a solution of SOCl<sub>2</sub> (2 mL) in 5 mL DCM. After the complete addition, four to five drops of DMF was added to this mixture and stirred it for 1 h at reflux temperature. The reaction progress was monitored by the TLC (9:1—petroleum ether:ethyl acetate), after complete conversion, distilled out the solvent in a rota-evaporator under reduced pressure to get the product.

*4-((5-(Difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)methyl)tetrazolo[1,5-a]quinolines (6a–e).* To the stirred solution of 5-(difluoromethoxy)-1H-benzo[d]imidazole-2-thiol **5** (10 mmol) in 20 mL of acetone was added K<sub>2</sub>CO<sub>3</sub> (15 mmol) stirred the contents for 10 min. To this solution, 4-(chloromethyl)tetrazolo[1,5-a]quinoline (10 mmol) was added and continued the stirring for 50 min at room temperature. The reaction progress was monitored by the TLC (8:2—petroleum ether:ethyl acetate), after complete conversion, the solvent was removed in a rota-evaporator under reduced pressure. The obtained product was purified by silica gel (60–120 mesh) column chromatographic technique using petroleum ether:ethyl acetate (8:2) as an eluent.

**Antibacterial activity.** All the compounds (**6a–e**) were screened for antibacterial activities against Gram positive *Bacillus subtilis*, *Staphylococcus aureus* (ATCC 6538), and Gram negative *Escherichia coli* (ATCC 8739), *Salmonella aboney* (NCTC 6017) bacteria using Streptomycin (Strept.) as a standard. Petri dishes and necessary glassware were sterilized in hot air oven (190°C, 45 min). The nutrient agar and saline (0.82% NaCl) were sterilized in autoclave (121°C, 15 psi, 20 min). Inoculum was prepared in sterile saline (0.82% NaCl) and the optical density of all pathogens was adjusted to 0.10 at 625 nm on a Chemito Spectrascan UV 2600 Spectrophotometer that is equivalent to 0.5McFarland Standards [15]. The nutrient

Table 2

Antibacterial activity of 4-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)methyltetrazolo[1,5-a]quinolines (6a-e).

Entry	Antimicrobial zone of inhibition (mm)							
	Gram positive				Gram negative			
	<i>Bacillus subtilis</i>		<i>S. aureus</i>		<i>E. coli</i>		<i>Salmonella aboney</i>	
	Conc. (mg/mL)	Conc. (mg/mL)	Conc. (mg/mL)	Conc. (mg/mL)	Conc. (mg/mL)	Conc. (mg/mL)	Conc. (mg/mL)	Conc. (mg/mL)
	10	20	10	20	10	20	10	20
6a	12	15	9	11	10	12	11	14
6b	11	13	10	14	14	15	13	16
6c	13	16	9	13	15	17	11	13
6d	10	13	7	10	13	15	10	13
6e	12	16	10	15	17	19	14	17
Strept.	18	-	19	-	22	-	20	-

agar plates were prepared by the pour plate method. The activity of the compounds was tested by disc diffusion method (paper disc method). All the bacterial cells were cultured in nutrient agar plates and the compounds to be tested were dissolved in *N,N*-dimethylformamide and were soaked on paper disc. The discs were placed into the plates and incubated at 37°C for 24 h. The diameter (mm) of the zone of inhibition around each disc was measured and results were recorded (Table 2).

**Spectroscopic data.** (3a) IR (KBr,  $\text{cm}^{-1}$ ): 3352 (OH), 1604 (C=C).  $^1\text{H}$  NMR ( $\text{CDCl}_3+\text{DMSO}-d_6$ , 300 MHz,  $\delta$  ppm): 5.20 (s, 2H,  $\text{CH}_2\text{-OH}$ ), 7.71 (t, 1H,  $J = 7.5$  Hz, Ar-H), 7.84 (t, 1H,  $J = 7.5$ , 7.8 Hz, Ar-H), 8.0 (d, 1H,  $J = 7.8$  Hz, Ar-H), 8.09 (s, 1H, Ar-H), 8.65 (d, 1H,  $J = 8.1$  Hz, Ar-H). ES-MS ( $m/z$ ): 201 (M + 1).

(4a) IR (KBr,  $\text{cm}^{-1}$ ): 1610 (C=C).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz,  $\delta$  ppm): 5.12 (s, 2H,  $\text{CH}_2\text{-Cl}$ ), 7.74 (t, 1H,  $J = 7.5$  Hz, Ar-H), 7.90 (t, 1H,  $J = 7.5$ , 7.8 Hz, Ar-H), 8.0 (d, 1H,  $J = 7.8$  Hz, Ar-H), 8.06 (s, 1H, Ar-H), 8.69 (d, 1H,  $J = 8.4$  Hz, Ar-H). ES-MS ( $m/z$ ): 219 (M + 1), 221 (M + 3).

(6a) IR (KBr,  $\text{cm}^{-1}$ ): 3241 (NH), 1606 (C=C).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz,  $\delta$  ppm): 4.98 (s, 2H, S- $\text{CH}_2$ ), 6.94–7.13 (m, 2H, O-CH-F and Ar-CH), 7.25 (s, 1H, Ar-CH), 7.44 (s, 1H, Ar-CH), 7.75 (t, 1H,  $J = 7.2$  Hz, Ar-CH), 7.92 (t, 1H,  $J = 7.2$  Hz, Ar-CH), 8.14 (d, 1H,  $J = 8.0$  Hz, Ar-CH), 8.28 (s, 1H, Ar-CH), 12.8 (s, 1H, NH). ES-MS:  $m/z$  399.1 (M + 1). Elemental analysis: Calc.: C: 54.27%, H: 3.04%, N: 21.09%. Found: C: 53.92%, H: 2.83%, N: 20.79%.

(6b) IR (KBr,  $\text{cm}^{-1}$ ): 3245 (NH), 1611 (C=C).  $^1\text{H}$  NMR ( $\text{CDCl}_3+\text{DMSO}-d_6$ , 300 MHz,  $\delta$  ppm): 2.54 (s, 3H,  $\text{CH}_3$ ), 4.99 (s, 2H, S- $\text{CH}_2$ ), 6.28–6.81 (td, 1H,  $J = 8.7$ , 66.6 Hz, O-CH-F), 6.96 (t, 1H,  $J = 6.6$  Hz, Ar-CH), 7.10 (s, 1H, Ar-CH), 7.27 (d, 1H,  $J = 8.4$  Hz, Ar-CH), 7.60–7.66 (m, 2H, Ar-CH), 8.06 (d, 1H,  $J = 5.1$  Hz, Ar-CH), 8.49 (d, 1H,  $J = 8.4$  Hz, Ar-CH), 12.25 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3+\text{DMSO}-d_6$ , 75 MHz,  $\delta$  ppm): 20.79 (Ar- $\text{CH}_3$ ), 30.91 (S- $\text{CH}_2$ ), 108.55 (Ar-C), 110.39 (Ar-C), 113.76 (Ar-C), 114.34 (Ar-C), 115.69 (Ar-C), 116.03 (Ar-C), 117.86 (Ar-C), 122.12 (Ar-C), 123.45 (Ar-C), 127.56 (Ar-C), 128.07 (Ar-C), 131.51 (Ar-C), 131.82 (Ar-C), 137.86 (Ar-C), 146.01 (Ar-C), 146.52 (Ar-C), 158.08 (O-CH-F<sub>2</sub>). ES-MS:  $m/z$  413.4 (M + 1). Elemental analysis: Calc.: C: 55.33%, H: 3.42%, N: 20.38%. Found: C: 55.02%, H: 3.09%, N: 20.01%.

(6d) IR (KBr,  $\text{cm}^{-1}$ ): 3250 (NH), 1606 (C=C).  $^1\text{H}$  NMR ( $\text{CDCl}_3+\text{DMSO}-d_6$ , 300 MHz,  $\delta$  ppm): 3.93 (s, 3H, O- $\text{CH}_3$ ), 4.98 (s, 2H, S- $\text{CH}_2$ ), 6.25–6.77 (td, 1H,  $J = 8.7$ , 66.0 Hz, O-CH-F), 6.98 (td, 1H,  $J = 2.1$ , 2.7 Hz, Ar-CH), 7.13 (d, 1H,  $J = 2.1$  Hz, Ar-CH), 7.22 (dd, 1H,  $J = 2.1$ , 2.7 Hz, Ar-CH), 7.39–7.46 (m, 1H, Ar-CH), 7.63 (d, 1H,  $J = 8.7$  Hz, Ar-CH), 8.02 (d, 1H,  $J = 7.2$  Hz, Ar-CH), 8.52 (d, 1H,  $J = 9.0$  Hz, Ar-CH), 12.16 (s, 1H, NH). ES-MS:  $m/z$  429.1 (M + 1). Elemental analysis: Calc.: C: 53.27%, H: 3.29%, N: 19.62%. Found: C: 52.96%, H: 3.03%, N: 19.28%.

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