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# SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME SUBSTITUTED PYRIDO [3′,2′: 4,5] FURO [2,3-*d*] PYRIMIDINE DERIVATIVES

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2-(3-Methoxyphenyl) pyrido [3′,2′: 4,5] furo [3,2-*d*] pyrimidin-4 (3*H*)-one **4** was synthesized using 2-chloro-3-cyanopyridine, which was converted to its cyclic iminochloride, followed by condensation with different amines and demethylation yielded novel substituted pyrido [3′,2′: 4,5] furo [2,3-*d*] pyrimidine compounds **6**a-i. The synthesized compounds were characterized by $^{1}$H NMR and $^{13}$C NMR spectroscopy. The synthesized compounds were screened for their antitubercular activities.

Pyrimidines are six membered heterocyclic ring compounds containing two nitrogen atoms. Pyrimidines are present among the three isomeric diazines. Several (mainly uracil, thymine and cytosine) pyrimidines have been isolated from the nucleic acids hydrolysis. The nucleic acids are essential constituent of all cells and thus of all living matter. Cytosine is found to be present in both types of nucleic acid i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), while uracil is present only in RNA and thymine only in DNA[1]. In addition to this, pyrimidine ring is also found in vitamin $B_1$, barbituric acid (2,4,6-trihydroxy pyrimidine) and its several derivatives (e.g. Veranal), which are used as hypnotics[2].

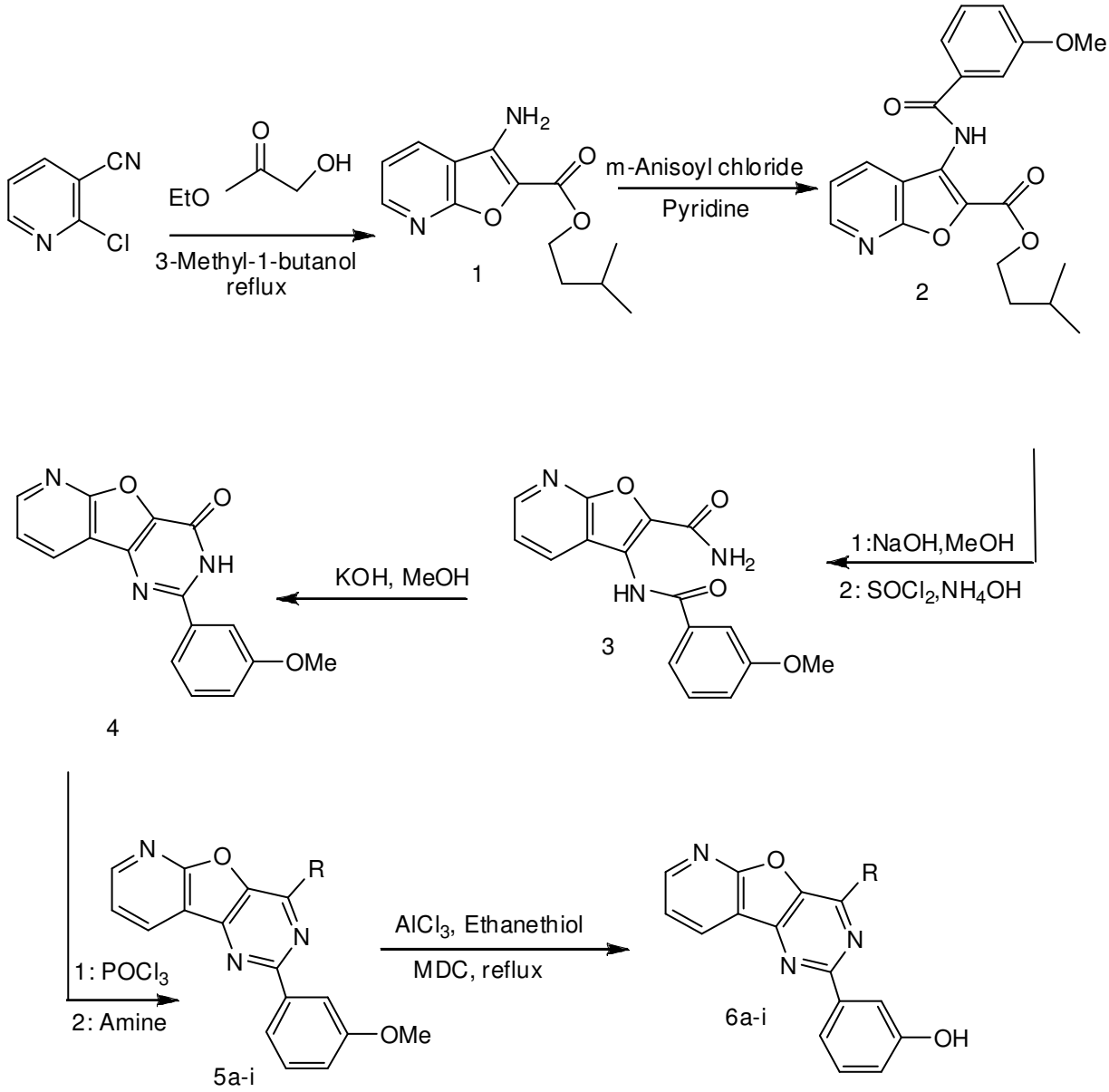
Pyrimidines, being an integral part of DNA and RNA exhibit diverse pharmacological properties[3] as effective bactericides, fungicides, vermicides, insecticides and medicides[4,5]. Certain pyrimidines and annulated pyrimidine derivatives are also known to display anticancer, antimalarial, antileishmanial and antifilarial activities[6-10]. Some furans are shown to be useful for the inhibition of thrombin formation[11]. Furans have also been extensively investigated for their pharmacological uses. Some heterocyclic systems constructed on furan, possess antihypertensive, antialleric and antidepressant activities[12-14].

Recently, furopyrimidines have been discovered as potent inhibitors of Tie-2 and VEGFR-2 receptor tyrosine kinases[15]. The biodynamic properties of these ring systems prompted us to design a system, which combines these bio-labile components in ring together to give compact structures for screening their antimicrobial activities. In addition, the furo [2,3-*d*] pyrimidine ring system is of biological interest due to the formal isoelectronic relationship between this ring and purine[16-19]. This observation led us to attempt the synthesis of some new furopyrimidine products with expected biological activity.

The starting key material, 2-chloro-3-cyano pyridine was condensed with ethylglyconate in 3-methyl-1-butanol and anhyd sodium carbonate to give transesterified compound **1** (confirmed by $^{1}$H NMR), which upon reaction with *m*-anisoyl chloride in pyridine gave corresponding amide **2**. Alkaline hydrolysis of compound **2** and the reaction of obtained acid with thionyl chloride followed by ammonium hydroxide gave corresponding bisamide **3**, which underwent cyclization in methanolic potassium hydroxide to produce 2-(3-methoxyphenyl) pyrido [3′,2′ : 4,5] furo [3,2-*d*] pyrimidin-4-(3*H*)-one **4**. Compound **4** was refluxed with phosphorus oxychloride to obtain cyclic iminochloride that upon condensation with various functionalised aliphatic and cyclic amines yielded novel substituted pyrido [3′,2′ : 4,5] furo [2,3-*d*] pyrimidines **5**a-i. Compounds **5**a-i were demethylated using $AlCl_3$/ethanethiol in dichloromethane resulting in corresponding hydroxy compounds **6**a-i, a useful toggle for the further pharmacological tweaking of these compounds, which is in progress and will be published later.

## Biological activity

Nine compounds from series were screened for their antitubercular activity according to standard




Compd :
5a, R=Methylamine
5b, R=Ethylamine
5c, R=Piperidine
5d, R=3-Cyano azetidine
5e, R=3-Methoxy pyrrolidine
5f, R=4-Piperidone
5g, R=Morpholine
5h, R=Piperazin-2-one
5i, R= Thiomorpholine

**SCHEME-1**

**Table-1**
**Antitubercular activity of substituted pyrido [3′,2′; 4,5] furo [2,3-*d*] pyrimidine derivatives**

| Compd | *M. tuberculosis* MTCC 200 (μg/ml) |
|---|---|
| 6a | 250 |
| 6b | 500 |
| 6c | >1000 |
| 6d | 62.5 |
| 6e | 100 |
| 6f | 250 |
| 6g | 250 |
| 6h | 250 |
| 6i | 200 |

protocol of L.J. Slope method. Antitubercular activity was carried out against *M. tuberculosis*. The standard strain *M. tuberculosis* $H_{37}$Rv is tested with each new batch of medium. The recommended drug concentrations are 4mg/l for streptomycin, 0.2mg/l for isoniazide, 40 mg/l for Rifampicin and 2 mg/l for ethambutol. Comparison of results are summarized in Table-1.

**Experimental**

All the melting points were determined in open glass capillary tubes and are uncorrected. Progress of reaction was monitored by thin layer chromatography (TLC) using silica gel-G coated aluminum plates (0.5 mm thickness, Merck) and spots were visualized under UV radiation, purified by crystallization and column chromatography. $^1$H NMR spectra and $^{13}$C NMR spectra (selected compounds) were recorded using $CDCl_3$ or DMSO-$d_6$ as a solvent and TMS as an internal reference and chemical shift values were expressed in δ ppm on a Bruker Avance-300 (300 MHz) and mass spectra on a Ion trap Perkin Elmer-1000 Mass spectrometer.

**Synthesis of isopentyl 3-aminofuro [2,3-*b*] pyridine-2-carboxylate 1.**

The suspension of 2-chloro-3-cyanopyridine (10.0g, 72.2 mmol), ethyl glycolate (10.51g, 101 mmol) and $Na_2CO_3$ (22.95g, 216.6 mmol) in 3-methyl-1-butanol (80 ml) was refluxed for 72 hr. The solvent was evaporated and water (100 ml) was added to the residue and obtained solid was dissolved in ethyl acetate (200 ml). The organic layer was washed with brine (75 ml), dried over sodium sulfate, filtered and concentrated to give off-white solid, which upon column chromatography over silica gel yielded compound **1** (3.2g, 21.5%, m.p. 112-114$^0$) as white solid. The product obtained was taken for the further steps. $^1$H NMR ($CDCl_3$, 300 MHz): 0.97 (d, *J*=6.5Hz, 6H), 1.73 (m, 2H), 1.84 (m, 1H), 4.40 (t, J=6.8Hz, 2H), 5.03 (bs, 2H), 7.25 (m, 1H), 7.94 (d, *J*=7.8 Hz, 1H), 8.49 (d, *J*=7.6Hz, 1H).

**Synthesis of isopentyl 3-(3-methoxybenzamido) furo [2,3-*b*] pyridine-2-carboxylate 2**

Dimethylamino pyridine (0.35g, 0.1 mmol) and *m*-anisoyl chloride (7.94g, 46.56 mmol) were added to the solution of compound **1** (6.4g, 31.04 mmol) in pyridine (40 ml). The reaction mixture was stirred at room temp for 18 hr and then concentrated. The residue was dissolved in chloroform (200 ml), washed with 1N HCl. The organic layer was dried over anhyd sodium sulfate, filtered and concentrated to give residue, which upon purification by column chromatography over silica gel gave compound **2**, m.p. 119-121$^0$ (4.8g, 45.5%) as yellow solid. The product obtained was taken for the next step. $^1$H NMR (DMSO, 300 MHz): 0.91 (s, 6H), 1.75 (m, 3H), 3.83 (s, 3H), 4.51 (t, 2H), 7.01-7.80 (m, 5H), 8.45 (d, 2H), 9.10 (s, 1H).

**Synthesis of 3-(3-methoxybenzamido) furo [2,3-*b*] pridine-2-carboxylic acid 3**

To a solution of compound **2** (4.8g, 14.1 mmol) in methanol (50 ml) was added 1M NaOH. The reaction mixture was stirred at room temp for 2 hr and then 1M HCl was added till pH 6.0. The precipitated solid was filtered to give the desired acid. To this solid, thionyl chloride (16.7g, 140 mmol) was added and the reaction mixture was refluxed for 2 hr, cooled to the room temp and then concentrated. The residue was dissolved in DMF (25 ml) and was added drop wise to the aq. ammonia (50 ml); the reaction mixture

was stirred at room temp for 2 hr. The water (100 ml) was added to the reaction mixture and was extracted with chloroform (75 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to give compound **3**, m.p. 130-131$^0$ (3.1g, 70.5%) as light brown solid. $^1$H NMR (DMSO, 300 MHz), 3.85 (s, 3H), 7.23 (d, *J*=7.3Hz, 1H), 7.45-7.53 (m, 4H), 8.07 (bs, 1H), 8.45 (bs, 1H), 8.50 (d, *J*=4.1 Hz, 1H), 8.78 (d, *J*=7.9 Hz, 1H), 11.2 (s, 1H).

**Synthesis of 2-(3-methoxyphenyl) pyrido [3′,2′: 4,5] furo [3,2-*d*] pyrimidin-4-(3*H*)-one 4**

To a solution of compound **3** (3.1g, 9.96 mmol) in methanol (25 ml) was added 2M KOH and the reaction mixture was stirred at 100$^0$ for 5 hr. The reaction mixture was cooled down to the room temp and conc. HCl was added. The solid obtained was dissolved in ethyl acetate (50 ml) and washed with brine, dried over anhyd sodium sulfate, filtered and concentrated to give residue which upon purification by column chromatography yielded compound **4**, m.p. 126$^0$ (2.7g, 93%) as white solid. $^1$H NMR (DMSO, 300 MHz), 3.85 (s, 3H), 7.13 (dd, $J_1$=8.2Hz, $J_2$=2.3 Hz, 1H), 7.45 (t, *J*=7.6Hz, 1H), 7.59 (m, 1H), 7.74 (m, 2H), 8.62 (m, 2H).

**Synthesis of compounds 5a-j : General procedure**

Phosphorus oxychloride (10 ml) was added to the compound **4** (1 mmol) and the reaction mixture was refluxed for 30 min. The reaction mixture was concentrated and azeotropically dried with toluene. Corresponding amine (2 mmol) was added to the obtained residue and was refluxed for 30 min. The reaction mixture was concentrated under reduced pressure; the residue was dissolved in chloroform (50 ml), washed with brine (50 ml), dried over sodium sulfate, filtered and concentrated to give residue. The obtained residues were purified by the column chromatography over silica gel to yield compound **5**a-i.

**Synthesis of compounds 6a-i : General procedure**

The solution of compound **5**a-i (0.5 mol) in MDC (15 ml) was added to the cold solution of aluminum chloride (6 mmol) and ethanethiol (6 mmol) under stirring. The reaction mixture was allowed to come to room temp and stirred for 2 hr. The reaction mixture was poured into water, acidified with dilute HCl and extracted with dichloromethane. The organic layer was washed with brine (3x15 ml), dried over sodium sulfate, filtered and concentrated to give crude material, which was purified by column chromatography over silica gel to yield compound **6**a-i.

**5**a: Yield 180mg, 56%, m.p. 122-125$^0$, $^1$H NMR (DMSO, 300 MHz) : 2.32 (6H, s), 3.87 (3H, s), 6.72 (1H, d, *J*=7.6Hz), 6.96 (1H, t, *J*=7.7Hz), 7.20 (1H, m), 7.30 (2H, m), 8.52 (2H, m). MS: m/z 321 (M+1).

**5**b: Yield 223mg, 64%, m.p. 128-129$^0$, $^1$H NMR (DMSO, 300 MHz): 1.02 (6H, t, *J*=7.3 Hz), 3.05 (4H, q, *J*=7.4Hz), 3.69 (3H, s), 6.82 (1H, d, *J*=7.7Hz), 6.94 (1H, t, *J*=7.6 Hz), 7.02 (1H, m), 7.27 (2H, m), 8.63 (2H, m). MS : m/z 349 (M+1).

**5**c: Yield 212mg, 59%, m.p. 120-122$^0$, $^1$H NMR (DMSO, 300 MHz), 1.30 (2H, m), 1.53 (4H, m), 2.73 (4H, m), 3.89 (3H, s), 6.76 (1H, d, *J*=7.6Hz), 6.89 (1H, t, *J*=7.6Hz), 7.07 (1H, m), 7.25 (2H, m), 8.41 (2H, m). MS : m/z 362 (M+1).

**5**d : Yield 203mg, 64%, m.p. 169-170$^0$, $^1$H NMR (DMSO, 300 MHz): 3.91 (3H, s), 4.17 (1H, m), 4.69-4.86 (4H, m), 7.14 (1H, d, *J*=7.9Hz), 7.50 (1H, t, *J*=7.9Hz), 7.69 (1H, m), 8.05 (2H, m), 8.78 (2H, m). MS: m/z 358 (M+1).

**5**e : Yield 210mg, 56%, m.p. 156-158$^0$, $^1$H NMR (DMSO, 300 MHz), 2.16 (2H, bs), 3.32 (3H, s), 3.84 (3H, s), 4.02-4.08 (4H, m), 4.17 (1H, bs), 7.03 (1H, dd, $J_1$=7.9Hz, $J_2$=2.4Hz), 7.41 (1H, t, *J*=7.9Hz), 7.58 (1H, dd, $J_1$=dd, $J_2$=5.5Hz), 7.96 (1H, bs), 8.02 (1H, d, *J*=7.8 Hz), 8.61 (2H, m). MS : m/z 378 (M+1).

**5**f: Yield 214mg, 57%, m.p. 163-165$^0$. $^1$H NMR (DMSO, 300 MHz), 2.65 (3H, t, *J*=5.8Hz), 3.34 (3H, s), 4.41 (4H, t, *J*=4.58Hz), 7.09 (1H, d, *J*=7.5Hz), 7.45 (1H, t, *J*=7.8Hz), 7.64 (1H, t, *J*=5.5Hz), 7.99 (2H, bs), 8.67-8.71 (2H, m). MS : m/z 375 [M+1].

**5**g: Yield 221mg, 61%, m.p. 158-159$^0$. $^1$H NMR (DMSO, 300 MHz), 3.90 (4H, t, *J*=4.6Hz), 3.92 (3H, s), 4.20 (4H, t, *J*=4.6Hz), 7.03 (1H, d, *J*=7.7Hz), 7.40 (1H, t, *J*=8.0Hz), 7.48 (1H, dd, $J_1$=7.4Hz, $J_2$=4.7Hz), 8.01-8.10 (2H, m), 8.58-5.59 (2H, m). MS: m/z 363 (M+1).

**5**h: Yield 251mg, 67%, m.p. 181-182$^0$. $^1$H NMR (DMSO, 300 MHz): 3.46 (2H, s), 3.85 (3H, s), 4.27 (2H, bs), 4.58 (2H, bs), 7.08 (1H, d, *J*=7.4Hz), 7.43 (1H, t, *J*=7.7Hz), 7.62 (1H, t, *J*=5.9Hz), 7.96 (1H, bs), 8.02 (1H, d, *J*=7.5Hz), 8.28 (1H, bs), 8.66 (2H, m). MS: m/z 376 (M+1).

**5**i: Yield, 268mg, 71%, m.p. 151-152$^0$. $^1$H NMR (DMSO, 300 MHz), 2.83 (4H, t, *J*=4.9Hz), 3.94 (3H, s), 4.52 (4H, t, *J*=4.9Hz), 7.03 (1H, dd, $J_1$=8.1Hz, $J_2$=2.3Hz), 7.41 (1H, t, *J*=7.9Hz), 7.47 (1H, dd, $J_1$=7.3Hz, $J_2$=5.2Hz), 7.89-8.06 (2H, m), 8.60-8.62 (2H, m). MS: m/z 380 (M+1).

**6**a: Yield 40%, 62mg, m.p. 198-201$^0$. $^1$H NMR (300 MHz, DMSO): 2.79 (6H, s), 6.85 (1H, d, *J*=7.6Hz), 7.30 (1H, t, *J*=7.8Hz), 7.65 (1H, m), 7.90 (2H, bs), 8.66 (2H, m), 9.64 (1H, bs). MS : m/z 329 {M+23 (Na)}.

**6**b: Yield 80mg, 48%, m.p. 207-210$^0$. $^1$H NMR (DMSO, 300 MHz): 0.98 (6H, t, *J*=7.2Hz), 2.98 (4H, q, *J*=7.2Hz), 6.89 (1H, d, *J*=7.8Hz), 7.28 (1H, t, *J*=8.1Hz), 7.69 (1H, m), 8.25 (2H, bs), 8.72 (2H, bs), 9.58 (1H, bs). MS : m/z 357 {M+23 (Na)}.

**6**c : Yield 82mg, 47%, m.p. 215-216$^0$. $^1$H NMR (DMSO, 300 MHz) : 1.25 (2H, m), 1.49 (4H, m), 2.75 (4H, m), 6.89 (1H, d, *J*=7.8Hz), 7.30 (1H, t, *J*=8.2Hz), 7.63 (1H, m), 7.88 (2H, m), 8.68 (2H, bs), 9.47 (1H, bs). MS : m/z 370 {M+23 (Na)}.

**6**d: Yield 87mg, 51%, m.p. 210$^0$. $^1$H NMR (DMSO, 300 MHz): 4.13 (1H, m), 4.65 (2H, m), 4.77 (2H, m), 6.88 (1H, d, *J*=7.5Hz), 7.30 (1H, t, *J*=8.0Hz), 7.64 (1H, m), 7.87 (2H, bs), 8.66 (2H, bs), 9.64 (1H, bs). MS : m/z 366 {M+23 (Na)}.

**6**e: Yield 76mg, 42%, m.p. 224-226$^0$. $^1$H NMR (DMSO, 300 MHz): 2.15 (2H, bs), 3.33 (3H, s), 4.01 (4H, m), 4.16 (1H, bs), 6.87 (1H, d, *J*=7.5Hz), 7.29 (1H, t, *J*=7.7Hz), 7.57 (1H, m), 7.87 (1H, d, J=7.4Hz), 7.89 (1H, s), 8.58 (2H, m), 9.53 (1H, s). MS : m/z 386 {M+23(Na)}.

**6**f: Yield 83mg, 46%, m.p. 234-236$^0$. $^1$H NMR (DMSO, 300 MHz): 2.65 (4H, bs), 4.41 (4H, bs), 6.88 (1H, d), 7.31 (1H, t, *J*=7.9Hz), 7.63 (1H, t, *J*=5.3Hz), 7.90 (2H, bs), 8.65 (2H, bs), 9.58 (1H, s). MS: m/z 383 {M+23(Na)}.

**6**g: Yield 84mg, 48%, m.p. 229-230$^0$. $^1$H NMR (DMSO, 300 MHz): 3.82 (4H, bs), 4.09 (4H, bs), 6.85 (1H, d, *J*=7.7Hz), 7.27 (1H, t, *J*=8.1Hz), 7.60 (1H, dd, $J_1$=7.6Hz, $J_2$=4.9Hz), 7.85 (2H, m), 8.63 (2H, m), 9.50 (1H, s). MS : m/z 371 {M+23(Na)}.

**6**h : Yield 95mg, 53%, m.p. 210-212$^0$. $^1$H NMR (DMSO, 300 MHz): 3.47 (2H, bs), 4.30 (2H, bs), 4.69 (2H, bs), 6.88 (1H, d, *J*=8.0Hz), 7.31 (1H, t, *J*=7.8Hz), 7.64 (1H, m), 7.98 (2H, bs), 8.29 (1H, s), 8.67 (2H, bs), 9.66 (1H, bs). MS : m/z 384 {M+23 (Na)}.

**6**i : Yield 89mg, 49%, m.p. 215-217$^0$. $^1$H NMR (DMSO, 300 MHz) : 2.85 (4H, bs), 4.40 (4H, bs), 6.88 (1H, d, *J*=7.90Hz), 7.30 (1H, t, *J*=8.0 Hz), 7.62 (1H, m), 7.87 (2H, bs), 8.65 (2H, m), 9.64 (1H, bs). MS : m/z 388 {M+23(Na)}.

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