Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2012, 4(3):1566-1572

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis, characterization and antimicrobial activity of substituted tetrahydrothieno [2,3-c]pyridin-2-yl)urea derivatives

Rushit Kalaria,*[1] Manish Mittal[2], Chetana Rajyaguru[1] and Jatin J. Upadhyay[1]

[1]*MVM Science and Home Science College, Saurastra University, Rajkot (Gujarat)*
[2]*School of Pharmaceutical Sciences, Jaipur National University, Jaipur (Rajasthan)*

ABSTRACT

As a part of systematic investigation of synthesis, characterization and biological activity of several new substituted Tetrahydrothieno [2,3-c]pyridin-2-yl)urea derivatives. (3a-3k) have been synthesized by well known chemical reaction of one active methylene containing moiety with a carbonyl function and Sulfur powder to give 2- Aminothiophene ring system followed by derivatization of amino into urea by mixed anhydride method. The structures of all the synthesized compounds have been determined by their spectral and micro analytical data. All the synthesized products were evaluated for their antibacterial activity against Bacillus substilis, Escherichia coli. Klebsiella pneumoniae and Streptococcus aureus bacteria and antifungal activity against Aspergillus niger fungi respectively. Most of the synthesized compounds exhibited significant anti-bacterial and anti-fungal activities.

Keywords: Sulphonamide, Thieno [2,3-c]pyridine, Urea, Sulphonamide, Arylureido, Antibacterial activity.

INTRODUCTION

Tetra hydro Thieno pyridine derivatives are known as bioactive molecules since very long time. Describes following thieno pyridine derivates as anti inflammatory and analgesic agents.[1-5] Thieno-pyridine derivatives anti-inflammatory properties and inhibiting effects on blood plate aggregation which make them therapeutically valuable.

It also describes their use in medicine as allosteric adenosine receptor modulators for uses including protection against hypoxia and ischemia induced injury and treatment of adenosine-sensitive cardiac arrhythmias.[6,8]

Toxicological investigation demonstrated the low toxicity and the good tolerance of the derivatives. The composition is usefully administrable for the treatment of the various stages of inflammation. It is applicable in chronic inflammatory rheumatism, degenerative rheumatism, in abarticular conditions, in oto-rhino-laryngology, in stomatology, in post-operative surgery and in traumatology.[9,10]

EXPERIMENTAL SECTION

The melting points were taken in open capillary tube and are uncorrected. The IR Spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB 104 with KBr pellets. The $_1$H-NMR (400 MHz) spectra were recorded on a Bruker 400 NMR spectrometer (with TMS as internal references). Mass spectra were recorded on

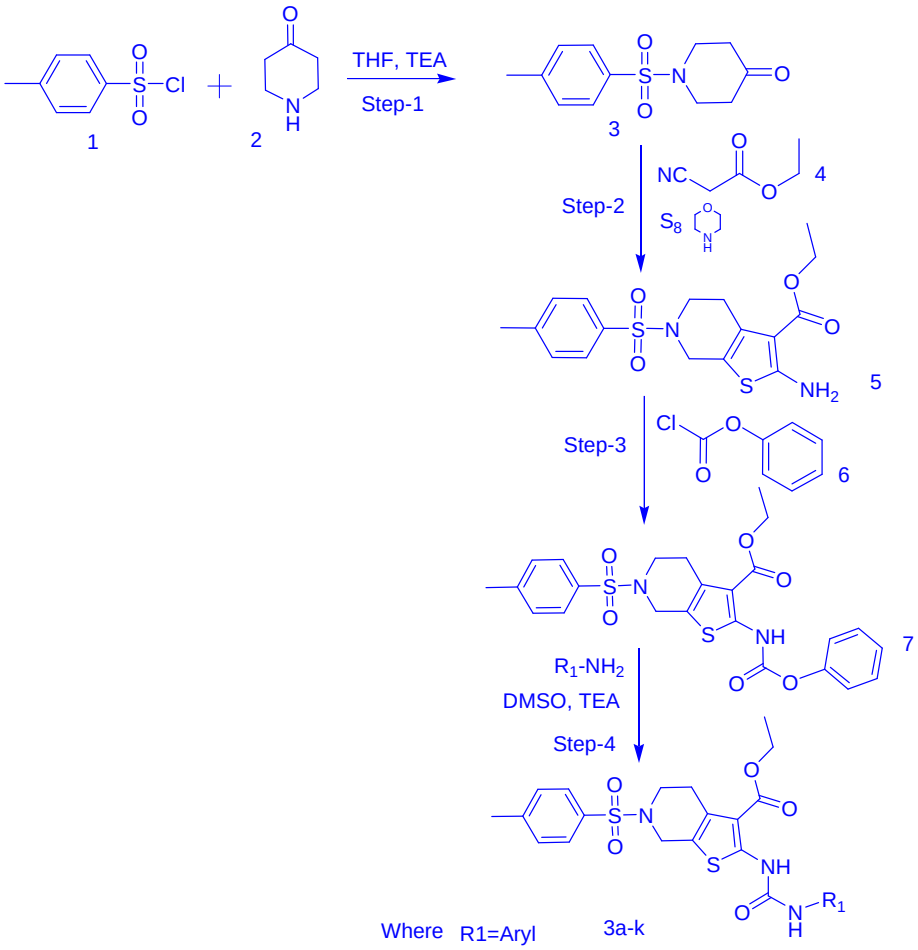
Shimadzu GC MS QP 5000. The purity of the compounds was checked by TLC on pre-coated SiO2 gel (HF254, 200 mesh) aluminium plates (E Merck) using Ethyl acetate and Hexane visualized in UV light. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallisation before use.

Anti-microbial screening

The anti-bacterial activity[11,12] of the synthesized compounds was tested against *Staphylococcus aureus (*ATCC 9144), *Escherichia coli (*ATCC 25922), *Pseudomonas aeruginosa* using nutrient agar medium (Hi-Media Laboratories, India). The antifungal activities[13] of the compounds were tested against *Aspergillus niger (* ATCC 9029) and *Aspergillus fumigatus* using sabouraud dextrose agar medium (Hi-Media Laboratories, India).

***Paper disc diffusion technique*:** The Sterilized 78 (autoclaved at 120°C for 30min) medium (40-50°C) was inoculated (1mL/100mL of medium) with the suspension (105cfu mL-1) of the micro-organism (matched to McFarland barium sulphate standard) and poured into a Petridis to give a depth of 3-4 mm. The paper impregnated with the test compounds (250µg/disc) was placed on the solidified medium. The plates were pre-incubated for 1 hr at room temperature and incubated at 37°C for 24 and 48 hrs for anti-bacterial and anti-fungal activities, respectively. Ciprofloxacin (100 µg/disc) and Fluconazole (100 µg/disc) were used as standard for anti-bacterial and anti-fungal activities, respectively.

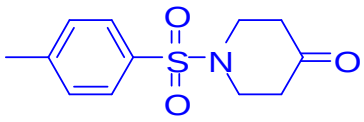
Synthetic scheme:



RESULTS AND DISCUSSION

(A) Chemistry

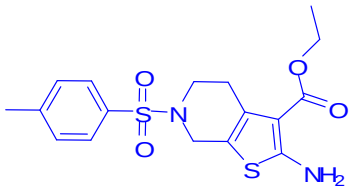
1. Synthesis of 1-[(4-methylphenyl) sulfonyl]-4-piperidinone (Intermediate-3).



General procedure for synthesis of (Int:3)

In RBF, 4-piperidinone hydrochloride (1.00 mol), THF and Triethylamine (2.5 mol) were charged. The reaction mixture was cooled to 0°C and 4-methyl phenyl sulfonyl chloride (1.05mol) was added portion wise to the reaction mixture at 0°C. The reaction mixture was allowed to warm at room temperature and stirred for 4 hours at same temperature. After the completion of reaction, Reaction mixture was concentrated under reduced pressure at 45°C. The crude was quenched with chilled water and stirred for thirty minutes. The obtaining solid was filtered and washed with water and dried. Yield: 85.00 %. M.P: 131°C, 1H NMR (solvent: $CDCl_3$) δ 7.72 (d, 2H, J=8.1 Hz), 7.38 (d, 2H, J=8.1 Hz) 3.42 (m, 4H), 2.58 (m, 4H), 2.42 (s, 3H).

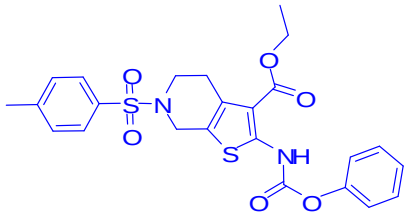
2. Synthesis of ethyl 2-amino-6-[(4-methylphenyl) sulfonyl]-4, 5, 6, 7- Tetra hydro thieno [2, 3-c] pyridine-3-carboxylate (Intermediate-5).



General procedure for synthesis of (Int:4)

In RBF, 1-[(4-methylphenyl) sulfonyl]-4-piperidinone (1.0 mol) (Intermediate-3), ethyl cyano acetate (1.10 mol), morpholine (5.0 mol) and sulfur (1.5 mol) was dissolved in ethanol at room temperature. The reaction mixture was heated at 70-80°C for 3-4 hours. After the completion of reaction, Reaction mixture was concentrated under reduced pressure at 45°C. The crude was quenched with chilled water and stirred for thirty minutes. The obtained solid was filtered and washed with water and dried. Yield: 70.00 %. M.P: 154°C. Elemental Analysis: Calculated: C (53.66%), H (5.30%), N (7.36%), Found: C (53.41%), H (5.19%), N (7.22%).

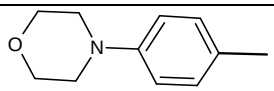
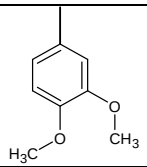
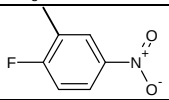
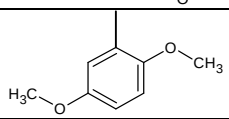
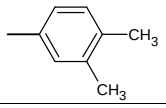
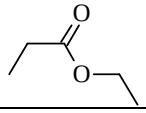
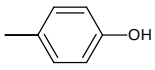
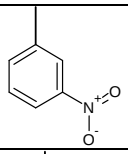
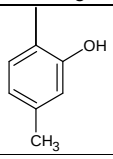
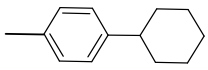
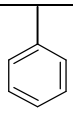
3. Synthesis of ethyl 6-[(4-methylphenyl)sulfonyl]-2-[(phenoxycarbonyl)amino]-4,5,6,7-tetrahydrothieno [2,3-c]pyridine-3-carboxylate (Intermeidate-7).



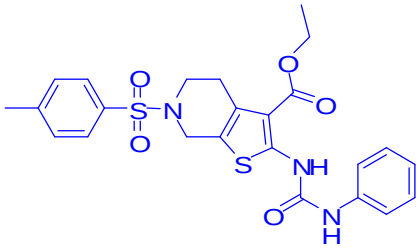
General procedure for synthesis of (Int:7)

In RBF, Intermediate-4 (1.0 mol) in THF, pyridine (1.05 mol) were charged at room temperature. Into the resulting reaction mixture Phenyl chloroformate (Intermediate-5) (1.05 mol) was added. The reaction mixture was stirred at room temperature for 2 hour. After the completion of reaction, Reaction mixture was cool at room temperature and concentrated under reduced pressure. The crude was quenched with chilled water. The obtained solid was filtered and washed with water and dried. Yield: 60.00 %. M.P: 142°C. Elemental Analysis: Calculated: C (57.58%), H (4.83%), N (5.60%), Found: C (57.30%), H (4.65%), N (5.32%).

TABLE-1: Physical constants of Ethyl-2-(3-arylureido)-6-[(4-methylphenyl) sulfonyl]-4, 5, 6, 7-tetrahydro thieno [2, 3-c] pyridine-carboxylates (3a-k)

Sr. No.	Substitution R	M Formula/ M.wt	M.P. °C	Yield %	% Composition Calcd./Found		
					C	H	N
3a		$C_{28}H_{32}N_4O_6S_2$ 584	184	67	57.52 57.44	5.52 5.43	9.58 9.51
3b		$C_{26}H_{29}N_3O_7S_2$ 559	194	68	55.80 55.72	5.22 5.17	7.51 7.43
3c		$C_{24}H_{29}N_4O_7S_2F$ 562	164	68	51.24 51.19	4.12 4.08	9.96 9.89
3d		$C_{26}H_{29}N_3O_7S_2$ 559	194	70	55.80 55.72	5.22 5.15	7.51 7.42
3e		$C_{26}H_{29}N_3O_5S_2$ 527	171	71	59.18 59.11	5.54 5.49	7.96 7.89
3f		$C_{22}H_{27}N_3O_7S_2$ 509	125	74	51.85 51.79	5.34 5.29	8.25 8.21
3g		$C_{24}H_{25}N_3O_6S_2$ 515	156	74	55.91 55.84	4.89 4.82	8.15 8.09
3h		$C_{24}H_{24}N_4O_7S_2$ 544	202	68	52.93 52.85	4.44 4.39	10.29 10.21
3i		$C_{25}H_{27}N_3O_6S_2$ 529	180	64	56.69 56.63	5.14 5.08	7.93 7.85
3j		$C_{30}H_{35}N_3O_5S_2$ 581	145	68	61.94 61.81	6.06 6.01	7.22 7.17
3k		$C_{24}H_{25}N_3O_5S_2$ 499	153	72	57.70 57.64	5.04 4.96	8.41 8.39

4. Synthesis of Ethyl-2-(3-(4-hydroxyphenyl) ureido)-6-[(4-methylphenyl) sulfonyl]-4, 5, 6, 7-tetrahydro thieno [2, 3-c] pyridine-carboxylates (3a-k).



General procedure for synthesis of (3a-k)

In RBF, ethyl 6-[(4-methylphenyl) sulfonyl]-2-[(phenoxycarbonyl) amino]-4, 5, 6, 7-tetrahydrothieno [2,3-c]pyridine-3-carboxylate (1.00 mol) was dissolved in DMSO. Triethylamine (2.50 mol) was added to the reaction mixture at room temperature. Into the resulting reaction mixture 4-amino phenol was added at room temperature. The reaction mixture was stirred for three hours at 60°C. After the completion of reaction, reaction mixture was quenched with chilled water. The obtained solid was filtered and washed with water and dried. The obtained product was purified by triturating with ethanol. Yield: 74.00 %. M.P: 156°C. Elemental Analysis: Calculated: C (55.91%), H (4.89%), N (8.15%), Found: C (55.84%), H (4.82%), N (8.09%).

Similarly, other compounds (3a-k) were synthesized by above mentioned process from intermediate: 7. the physical data are recorded in Table-1.

(B) Anti-microbial screening

Table 2: Antibacterial Activity of the newly synthesized compounds

Compound Name	Antibacterial activity			
	S. aureus		***B.Subtilis***	
S.No.	**1000*(µg/ml)***	**500*(µg/ml)***	**1000*(µg/ml)***	**500*(µg/ml)***
3a	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3b	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3c	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3d	**+Ve**	**-Ve**	**+Ve**	**+Ve**
3e	**+Ve**	**-Ve**	**+Ve**	**-Ve -**
3f	**+Ve**	**-Ve**	**+Ve**	**+Ve**
3g	**+Ve**	**-Ve**	**+Ve**	**+Ve**
3h	**+Ve**	**-Ve**	**+Ve**	**+Ve**
3i	**+Ve**	**-Ve**	**+Ve**	**+Ve**
3j	**+Ve**	**-Ve**	**+Ve**	**-Ve**
3k	**+Ve**	**-Ve**	**+Ve**	**-Ve**
Ciprofloxacin	**+Ve**	**+Ve**	**+Ve**	**+Ve**

**Concentration of standard Ciprofloxacin (100 µg/disc) and Fluconazole (100 µg/disc).*

Table 3: Antifungal Activity of the newly Synthesized Compounds

Compound Name	Antifungal activity			
	A.niger		***C. albicans***	
S.No.	**1000*(µg/ml)***	**500*(µg/ml)***	**1000*(µg/ml)***	**500*(µg/ml)***
3a	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3b	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3c	**+Ve**	**-Ve -**	**+Ve**	**-Ve -**
3d	**+Ve**	**-Ve -**	**+Ve**	**-Ve -**
3e	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3f	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3g	**+Ve**	**-Ve -**	**+Ve**	**-Ve -**
3h	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3i	**+Ve**	**-Ve -**	**+Ve**	**+Ve**
3j	**+Ve**	**+Ve**	**+Ve**	**+Ve**
3k	**+Ve**	**-Ve -**	**+Ve**	**-Ve -**
Fluconazole	**+Ve**	**+Ve**	**+Ve**	**+Ve**

**Concentration of standard Fluconazole (100 µg/disc).*

CONCLUSION

We successfully synthesize more the 11 new substituted Tetrahydrothieno [2,3-c]pyridin-2-yl)urea derivatives. All compounds were characterized for their structure by 1HNMR and found correct.

The newly synthesized organic compounds were screened through two different types of screening i.e. (1) Primary Screening using 1000 µg/ml conc. (2) Secondary Screening 500 µg/ml to 250 µg/ml conc. The compounds which were active against the microbes in primary screening were further taken for the secondary screening.

From the results of experiments using newly synthesized organic compounds' it is clear that all the compounds were moderately active at lower dilution i.e. high concentration like 1000 µg/ml conc. of compounds. In the series 3a-k almost three compounds 3a, 3b and 3c were found active at 500 µg/ml conc. against *staphylococcus aureus. Bacillus Subtilis* was inhibited at 500 µg/ml conc. by eight compounds 3a, 3b, 3c, 3d, 3f, 3g, 3h, and 3i. Three compounds 3a, 3b and 3c were active against both cultures *B.Subtilis* and *S.aureus*.

For fungi in the series 3a-k almost six compounds 3a, 3b, 3e, 3f, 3h, and 3j were found active at 500 µg/ml conc. against *A. niger*. *C. albicans* was inhibited at 500 µg/ml conc. by seven compounds i.e. 3a, 3b, 3e, 3f, 3h, 3i and 3j.

Acknowledgement
Authors are thankful to Department of chemistry, MVM Science & Home Sciences College, Rajkot. for giving me opportunity to perform all presented work and support me in my research work. The authors also sincerely acknowledge the constant help and encouragement provided by the Head of department K. J. Ganatra and DNC Pharmaceuticals Ahmedabad, during this work for providing laboratory facilities.

REFERENCES

[1].Baker, William L.; White, C. Michael; *American Journal Cardiovascular Drugs*: **2009**, 213-229.
[2].Kurt Huber, Uma Yasothan, Bashar Hamad & Peter Kirkpatrick; *Nature Reviews Drug Discovery* **2009**, (8) 449-450.
[3].Megumi Taniuchi, MD, PhD; Howard I. Kurz, MD; John M. Lasala, MD, PhD; Circulation. **2001**, (104) 539-543
[4].Henrik Sune Andersen, Ole H. Olsen, Lars F. *J. Med. Chem*., (**2002**), 45 (20), 4443–4459
[5].Diane H. Boschellia, Biqi Wua, Ana Carolina Barrios Sosaa, , Joan J. Chena, Jennifer M. Golasb and Frank Boschellib; *Bioorganic & Medicinal Chemistry Letters*; **2005**, 4681-4684
[6].Alice Maria Rolim Bernardinoa, Luiz Carlos da Silva Pinheiroa, *Bioorganic & Medicinal Chemistry;* **2006**, (14), 5765-5770.
[7].L.Nathan Tumeya, Diane H. Boschellia, Julie Leeb and Divya Chaudharyb; *Bioorganic & Medicinal Chemistry Letters*; **2008**, (18) 4420-4423.
[8].Fawzy A. Attaby a; M. A. A. Elneairy a;M. S. Elsayed a; *Phosphorus, Sulfur, and Silicon and the Related Elements,* **1999**, (149) 49 – 64
[9].Alain Heymes, Jean-Pierre Maffrand, US4, 065,460
[10].Kling, Andreas; Lange, Udo E. W.; Mack, Helmut; Bakker, et al. *Bioorganic & Medicinal Chemistry Letters*, **2005**, 5567 – 5573
[11].Hussein El-Kashef 1, Abdel-Rahman Farghaly 1, *Molecules* **2010**, (15) 2651-2666.
[12].Parmar, Kokila; Suthar, Bharat; Suthar, Arun; Maheta, Abhay; *Journal of Heterocyclic Chemistry*; **2009**, (46) 975 – 979
[13].Satake, Kyosuke; Imai, Toshiyuki; Kimura, Masaru; Morosawa, Shiro; *Heterocycles*; **1981**, (16) 1271- 1274
[14].Angell, Richard M.; Atkinson, Francis L.; Brown, Murray J.; et al.; *Bioorganic & Medicinal Chemistry Letters*; **2007**, (17) 1296 -1301
[15].Faltz, Heike; Bender, Christoph; Liebscher, Juergen; Synthesis; **2006**; 2907-2922.
[16].Baraldi, Pier Giovanni; Zaid, Abdel Naser; Lampronti, Ilaria; *Bioorganic & Medicinal Chemistry Letters;* **2000**, (10)1953 – 1958.
[17].Parmar, Kokila; Suthar, Bharat; Suthar, Arun; Maheta, Abhay; *Journal of Heterocyclic Chemistry*; vol.46; **2009**, (5) 975 – 979
[18].Angell, Richard M.; Atkinson, Francis L.; Brown, Murray J.; et al.; *Bioorganic & Medicinal Chemistry Letters*; **2007,** (17) 1296 – 1301.
[19]. I.O Adeoye, O.O Adelowo, and Onawumi, *Journal of chemical and Pharmaceutical research* **2012**, 4(1):1-5

[20]. Shilpi Gupta, Shikha Gupta, Hemant Kulshrashtha, *Journal of chemical and Pharmaceutical research* 2012, 4(1):75-77
[21]. T.M. Bhagat, D.K. Swamy, M.N. Deshpande, *Journal of chemical and Pharmaceutical research* **2012**, 4(1):100-104
[22]. Manu Seth, Pramilla Sah, *Journal of chemical and Pharmaceutical research* **2012**, 4(1):146-153