

Synthesis, physicochemical characterization and analgesic evaluation of some new thieno [2,3-*D*] Pyrimidin 4(3*H*) one derivatives

Dinesh P Kawade^{1*}, Dinesh R Chapple², Pramod B Khedekar³

¹Associate Professor, ²Professor and Principal, ³Professor, ^{1,2}Dept. of Pharmaceutical Chemistry, ³Dept. of Pharmaceutical Sciences, ^{1,2}Priyadarshini J. L. College of Pharmacy, Nagpur, Maharashtra, ³Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra, India

*Corresponding Author: Dinesh P Kawade

Email: drdinesh03@gmail.com

Abstract

A POCl₃ catalyzed, efficient, one-step and solvent-free synthesis of novel thieno [2,3-*d*] pyrimidin-4(3*H*)-one derivatives from 2-amino-4,5-substitutedthiophene-3-carbonitrile has been developed using various aliphatic acid under both conventional heating and microwave irradiation techniques. The formation of compounds was confirmed via elemental analysis and spectroscopic techniques like FTIR, ¹HNMR and mass spectroscopy. All synthesized compounds have been screened for their analgesic activity by using Eddy's hot plate method. The synthesized compounds 2d, 2k and 2h showed good analgesic activity and compounds 2a, 2b, 2g and 2i showed moderate whereas remaining compounds possessed less analgesic activity compared with standard, Tramadol.

Keywords: POCl₃, Thieno[2,3-*d*]pyrimidin-4 (3*H*)-one, Analgesic activity, Eddy's hot plate.

Introduction

Medication revelation is ceaseless and iterative process, which begin with the recognizable proof of lead atom of wanted natural activity (lead age and closures with the streamlining of this lead (lead advancement) for choice of new hopeful particle in sedate improvement.¹ The attention to synthetic, physical physiological, biochemical properties, receptor locales, SAR and stereochemistry and so on is extremely huge in sedate plan for the fruitful advancement of medication particle.² Since, sedate plan is a coordinated for building up the train which forecasts a time of adjusted medication, a medication lacking symptom. It looks to clarify impacts of natural structure or its physicochemical properties included.³ It examines the procedures by which the medication s delivered their belongings; how they respond with the cellular material of inspire a specific pharmacological impact or reaction. How they changed or detoxified, used or disposal by living being.⁴ These ideas are the building stones whereupon the structure of medication configuration in assembled. The various new advancements have been created and connected in tranquilize innovative work (R&D) to abbreviate the examination cycle and to decrease the costs⁵. Among them, computational methodologies have upset the pipeline of disclosure and advancement over the most recent 40 year, computational advances for medicate R&D have advanced rapidly, particularly in late decades with the extraordinary improvement of science, biomedicine, and PC ability.⁶ The computational instruments have been connected in relatively every phase of medication R&D, which have incredibly changed the system of medication disclosure.⁷ Aggravation is a neighborhood response of the vascular and supporting components of a tissue to damage bringing about the arrangement of protein-rich exudates; it is defensive reaction of the non particular insusceptible framework that serve to limit, kill, or to crush a harmful operator in planning for the way toward recuperating. The indication of aggravation are

rubor (redness), calor (warm), dolor (pain), tumor (swelling), and functio laesa (loss of function).⁸ Agony is an attributes neurophysical sensation emerging from a harmful boost.⁹ It is isolated into integumental agony (i.e. shallow, identified with skin, muscle and joints) and instinctive torment (i.e. Deep situated, related to heart, stomach, kidney and rankle bladder). Nonsteroidal calming drug and broadly utilized for the treatment of different incendiary infections and also to remember the hurts and agony.¹⁰ They apply their restorative impact through down control of prostaglandin blend by restraining the rate restricting cyclooxygenase (COX) catalyst engaged with the provocative course.¹¹ Despite the fact that this medication are for the most part all around endured in understanding with joint condition, a high frequency of gastrointestinal symptom, for example, mucosal injury, discharge, and ulceration has been a significant issue in their medicine. These present helpful insufficiencies force the need to create more secure medication.¹²

An analgesics or painkillers are 'agents that relieve pain by elevating the pain threshold without disturbing consciousness or altering sensory-modalities'. Besides 'pain' may also be defined in psychological perspective as 'a particular type of sensory experience distinguished by nerve tissue from sensations, such as: touch, heat, pressure and cold.'¹³

Thiophene containing compounds are well known to exhibit various biological effects. Heterocycles containing the thienopyrimidine moiety are of curiosity because of their interesting pharmacological and biological activities.²⁰⁻²² They bear structural analogy and isoelectronic relation to purine and several substitutedthieno[2,3-*d*] pyrimidine derivatives shown to exhibit prominent and versatile biological activities.²³⁻²⁴ Over the last two decades, many thienopyrimidines have been found to exhibit a variety of synthesized as potential anticancer,²⁵ analgesic,²⁶ antimicrobial^{27,28} and antiviral agents.²⁹

Recently, we reported some reviews on pyrimidinethiones³⁰ and condensed pyrimidines, namely pyrazolo-pyrimidines³¹ and furopyrimidines.³² The work deals with the study of the synthesis, reaction and biological application of thienopyrimidines in view of their great importance. In the last decade, thienopyrimidines were reviewed.³³ The three fundamental thienopyrimidines systems are thieno[2,3-*d*] pyrimidine (I), thieno[3,2-*d*] pyrimidine (II) and thieno[3,4-*d*] pyrimidine (III). This article aimed to show the recent novel precursors to synthesize thienopyrimidine derivative and reported their application in pharmaceutical and biological evaluations in the last decade.³⁴⁻³⁶ Various synthetic approaches have been utilized for the synthesis of thienopyrimidines. Recently, Bakavoli et al. used molecular iodine as an oxidising agent for the synthesis of thienopyrimidines via an oxidative heterocyclization reaction. However, the synthesis of thienopyrimidine from 2-amino-4, 5-substitutedthiophene-3-carbonitrile requires two steps and solvent-free method to generate a series of thieno[2,3-*d*] pyrimidin-4(3H)-one derivatives. In recent times, microwave assisted synthesis of medicinal compounds has gained appreciation among the synthetic chemists due to their improved selectivity, shorter reaction time, eco-friendliness and superior work-up procedures. Microwave has been used to speed up chemical reactions in the laboratories which led scientists to investigate the mechanism of microwave dielectric heating and to identify the advantages of the technique for chemical synthesis.³⁶

Experimental

Materials and Methods

All the chemicals and solvents used were of AR and LR grade, obtained from Loba, Merck and Fisher scientific fine chemicals (Mumbai, India). The progress of reaction was tested on precoated silica gel G plates obtained from Merck, using the mobile phase toluene and ethyl acetate in 7:3 ratio. Iodine chamber and UV lamp ($\lambda = 254$ nm) were used for visualization of the spots. LABHOST melting point apparatus was used for measurement of melting points in a capillary tube and are uncorrected. The IR spectra (ν_{\max} , cm^{-1}) were recorded on Shimadzu FT-IR IRA-Affinity-1 spectrophotometer as KBr pellet technique. ¹HNMR (δ , ppm) spectra were recorded on Bruker Avil-400 MHz spectrophotometer. ¹HNMR spectra for synthesized compound were recorded with CDCl_3 as solvent. Mass spectra were recorded on water UOLC-TQD (ESI-MS & APCI-MS).

General procedure for preparation of 2-amino-4, 5-substitutedthiophene-3-carbonitrile (scheme 1)(1a-1h)

Take a mixture of substituted ketones (1a-1g) (0.01M), malanonitrile (0.01M), sulfur (0.01M) and ethanol (10.0mL) were mixed in a conical flask. The reaction mixture was warmed up to 40-50°C on a water bath and then diethylamine (1.0mL) was added with constant stirring in such a way that the temperature does not exceed 50°C. Stirring was continued for 1-2h till solid crystals get separated. The reaction mixture was then cooled and kept in a refrigerator. The fine

crystals thus obtained were filtered. Dried and recrystallized from ethanol to give compounds.

General procedure for preparation of thieno[2,3-*d*]pyrimidin-4(3H)-one derivatives (scheme 2)(2a-2k)

Conventional synthesis

2-Amino-4,5-substitutedthiophene-3-carbonitrile (1a-1h) (1mM) was dissolved in appropriate aliphatic acid (2.0mL). Then POCl_3 (0.2mL) was added drop wise and the reaction mixture has been kept for reflux on a boiling water bath. After completion of the reaction, the mixture was poured on ice-cold water (50.0mL) and crude precipitates thus formed were filtered, washed with 10% sodium bicarbonate solution, dried and recrystallized from ethanol.

Microwave assisted synthesis

A mixture of 2-amino-4, 5-substitutedthiophene-3-carbonitrile (1a-1h) (1mM) and alumina (0.5 g) were finally crushed and transferred to a glass vial and then phosphorus oxychloride (0.2mL) was added. The glass vial was then capped and microwaves were irradiated in a microwave oven SAMSUNG (Self fabricated microwave analyzer) at a power of 180W for 2-4 mins. After the completion of reaction, the mixture was poured on ice-cold water (50.0mL). The precipitated product was filtered and washed with 10% sodium bicarbonate solution to give the desired compounds.

Synthesis of 6-ethyl-2,5-dimethylthieno-[2,3-*d*] pyrimidin-4(3H)-one

IR(KBr, cm^{-1}): 1.31, multiplet (t, 3H, $-\text{CH}_3$), 0.9 singlet (3H, $-\text{CH}_3$), 4.7. Singlet (N-H), 7.46 singlet (Heterocyclic amine); MS: m/z 208 (100%, M^+)

Synthesis of 6-(2-hydroxyphenyl)-2,5-dimethylthieno[2,3-*d*]pyrimidine-4(3H)-one

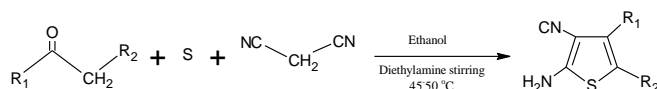
IR(KBr, cm^{-1}): 3413.19 (N-H stretch), 1214.04 ($-\text{OH}$), 1106.12 (C-S), 1633.7 (C=O), 1666.80 (C=N), ¹HNMR (CDCl_3 , δ): (t, 3H, $-\text{CH}_3$), 0.9 singlet, (Aryl-OH) 4.40 multiplet, (N-H) 4.6 singlet, (Heterocyclic amine) 7.30 singlet; MS (m/z). 272 (100%, M^+)

Synthesis of 7-Methyl-4-oxo-3,4,5,6,7,8-hexahydro[1] benzothieno [2,3-*d*]pyrimidin-2-yl- acetic acid.

IR (KBr, cm^{-1}): (C- CH_3 stretch) 1390.84, (C=O) 1566.28,

$\text{H}_2\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$ 1177.59, (thiophene) 954.50, ($\text{C}=\text{NH}$) 1490.07, ¹HNMR (CDCl_3 , δ): (t, 3H, $-\text{CH}_3$) 1.09 doublet, (N-H) 4.5 Singlet, (Heterocyclic amine) 7.23 Singlet, (Acids), 2.60 Multiplet; MS: (m/z) 278 (100% M^+)

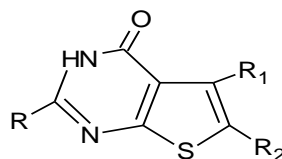
Synthetic scheme



Substituted ketones, Sulfur, Malanonitrile

2-Amino-4, 5-substituted

thiophene-3-carbonitrile (1a-1h)

Thieno[2,3-*d*]pyrimidin-4(3*H*)- one derivatives (2a-2k)

Method 1 : POCl₃, Reflux
1-2 hrs (70-80%)
(conventional synthesis)
Method 2 : Al₂O₃, POCl₃,
MW irradiation 5-7 mins
(78-90%)

RCOOH
(aliphatic acids)

**Table 1:** Synthesized compound of thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives

S. No	Compound Code	R	R ₁	R ₂
1	2a	-CH ₃		
2	2b	-CH ₃	-CH ₃	C ₂ H ₅
3	2c	-CH ₃	-CH ₃	
4	2d	-CH ₃	-CH ₃	
5	2e	-CH ₃	-CH ₃	
6	2f			
7	2g	-H	-CH ₃	
8	2h			
9	2i	-H	-CH ₃	
10	2j	-H	-CH ₃	
11	2k	-CH ₃	-CH ₃	

Results & Discussion

Table 2: Physicochemical properties of 2-amino-4,5-substitutedthiophene-3carbonitrile (1a-1h)

Comp. Code	Compound name	Molecular formula	Molecular weight (g)	% yield	R _f Value	Melting point °C
1a	2-amino-6-methyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile	C ₁₀ H ₁₂ N ₂ S	192.28	90.00	0.86	166-167
1b	5-ethyl-3-isocyano-4-methylthiophen-2-amine	C ₈ H ₁₀ N ₂ S	166.24	78.23	0.85	162-163
1c	2-(5-amino-4-isocyano-3-methylthiophen-2-yl)phenol	C ₂ H ₁₀ N ₂ OS	230.28	66.20	0.83	160-161
1d	5-(4-bromophenyl)-3-isocyano-4-methylthiophen-2-amine	C ₁₂ H ₉ BrN ₂ S	293.182	85.75	0.82	163-164
1e	3-isocyano-4-methyl-5-(4-nitrophenyl)thiophen-2-amine	C ₁₂ H ₉ N ₃ O ₂ S	259.284	78.67	0.87	157-158
1f	3-isocyano-4-methyl-5-phenylthiophen-2-amine	C ₁₂ H ₁₀ N ₂ S	214.28	87.35	0.93	155-156
1g	4-(5-amino-4-isocyano-3-methylthiophen-2-yl)phenol	C ₁₂ H ₁₀ N ₂ OS	230.28	77.80	0.81	161-162
1h	5-(4-aminophenyl)-3-isocyano-4-methylthiophen-2-amine	C ₁₂ H ₁₁ N ₃ S	229.30	89.70	0.84	189-161

Table 3: Physicochemical properties of Thieno[2,3-*d*]pyrimidine-4(3*H*)derivatives (2a-2k)

Compd Code	Compound Name	Molecular Formula	Molecular weight (g)	Melting Point °C	% Yield	R _f Value
2a	2,8 dimethyl-5,6,7,8-tetrahydrobenzo-[4,5]thieno[2,3- <i>d</i>]pyrimidin-4(3 <i>H</i>)-one	C ₁₂ H ₁₄ N ₂ OS	234.31	203-204	86.00	0.83
2b	6-ethyl-2,5-dimethylthieno[2,3- <i>d</i>]pyrimidin-4(3 <i>H</i>)-one	C ₁₀ H ₁₂ N ₂ OS	208.28	204-205	84.26	0.85
2c	6-(2-hydroxyphenyl)-2,5-dimethylthieno [2,3- <i>d</i>] pyrimidin-4(3 <i>H</i>)-one	C ₁₄ H ₁₂ N ₂ O ₂ S	272.34	206-207	82.75	0.90
2d	6-(4-bromophenyl)-2,5-dimethylthieno[2,3- <i>d</i>] pyrimidin-4(3 <i>H</i>)-one	C ₁₄ H ₁₁ BrN ₂ O S	335.21	209-210	80.33	0.93
2e)	2,5-dimethyl-6-(4-nitrophenyl)thieno[2,3- <i>d</i>]pyrimidin-4(3 <i>H</i>)-one	C ₁₄ H ₁₁ N ₃ O ₃ S	301.32	207-208	80.65	0.89
2f	2,3-dihydroxy-3-(7-methyl-4-oxo-3,4,5,6,7,8-hexahydro[1] benzothieno[2,3- <i>d</i>] pyrimidin-2-yl) propanoic acid	C ₁₄ H ₁₆ N ₂ O ₅ S	324.35	210-211	68.22	0.79
2g	5-methyl-6-phenylthieno-[2,3- <i>d</i>]pyrimidin-4(3 <i>H</i>)-one	C ₁₃ H ₁₀ N ₂ OS	242.29	203-204	82.52	0.82
2h	7-methyl-4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3- <i>d</i>]pyrimidin-2-yl)acetic acid	C ₁₃ H ₁₄ N ₂ O ₃ S	278.32	198-199	66.15	0.83
2i	5-Methyl-6-phenyl thieno[2,3- <i>d</i>]pyrimidin-4(3 <i>H</i>)-one	C ₁₃ H ₁₀ N ₂ OS	242.29	196-197	72.35	0.88
2j	6-(4-hydroxyphenyl)-5-methylthieno[2,3- <i>d</i>]pyrimidin-4(3 <i>H</i>)-one	C ₁₃ H ₁₀ N ₂ O ₂ S	258.29	203-204	80.42	0.92
2k	6-(4-aminophenyl)-2,5-dimethylthieno[2,3- <i>d</i>]pyrimidin-4(3 <i>H</i>)-one	C ₁₄ H ₁₃ N ₃ OS	271.33	209-209	83.00	0.79

Pharmacological Screening

Animal

The healthy Swiss Albino mice of either sex of weight 14-25g were selected for their analgesic activity. Animals were housed in standard condition of temperature 22°C (\pm 3°C) and relative humidity (30-70%) with 12:12 light: dark cycle. Study protocol was approved by Institutional Animal Ethical Committee for the purpose of Control and supervision on Experimental Animals (IAEC, Approved No. 648/PO/Ere/S/02/CPCSEA) before experiment. The animals were fed with standard diet (pellets) and were *ad libitum*.

Analgesic activity (Eddy's Hot Plate Method)

Swiss albino mice of either sex were divided into fourteen different groups each containing six animals, the animals were marked on tail individually. Food was withdrawn 12 h

prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. To control group (0.3 mL) 1% v/v solution of DMSO, standard group (Tramadol, dose: 20mg/kg), and test groups Compound (2a-2k), dose, dose:20mg/kg) were given by oral route and after 0 min and 90 min. The percentage inhibition in analgesic activity was evaluated using the following formula.

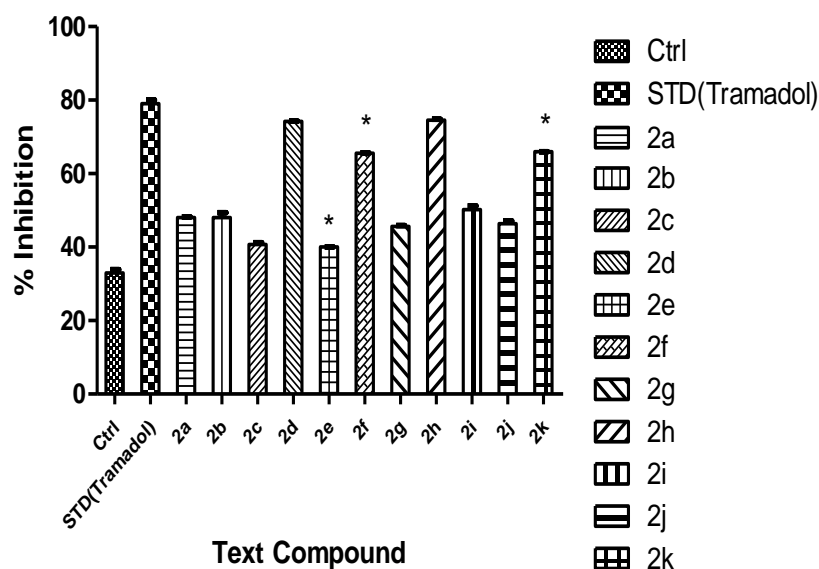
$$\% \text{ inhibition} = [1 - (\text{before treatment} / \text{after treatment})] \times 100$$

The analgesic activity was performed by hot plate method on Swiss albino mice by giving dose 20mg/kg of synthesized derivative.

Table 4: Analgesic activity of synthesized compounds (2a-2k)

Compounds	Mean Latency		% Inhibition
	0 Min	After 90 Min	
Ctrl	1.033 \pm 0.010	1.54 \pm 0.52	32.92 \pm 0.98
STD (Tramadol)	1.02 \pm 0.013	4.87 \pm 0.38	79.05 \pm 0.96
2a	1.063 \pm 0.016	2.046 \pm 0.019	48.04 \pm 0.15
2b	1.54 \pm 0.050	1.04 \pm 0.022	48.07 \pm 1.27
2c	1.21 \pm 0.038	2.04 \pm 0.092	40.68 \pm 0.50
2d	1.04 \pm 0.026	4.03 \pm 0.028	74.19 \pm 0.071
2e	1.03 \pm 0.023	1.05 \pm 0.022	40.00 \pm 0.045
2f	1.04 \pm 0.031	3.02 \pm 0.029	65.56 \pm 0.068
2g	1.045 \pm 0.015	1.098 \pm 0.022	45.61 \pm 0.27
2h	1.025 \pm 0.016	4.023 \pm 0.027	74.52 \pm 0.27
2i	1.19 \pm 0.018	2.06 \pm 0.39	50.24 \pm 0.95
2j	1.11 \pm 0.19	2.07 \pm 0.09	46.37 \pm 0.78
2k	1.04 \pm 0.023	3.05 \pm 0.024	65.90 \pm 0.041

Graph 1



Analgesic activity of synthesized compounds (2a-2k)

Analgesic activities of synthesized compound were studied using hot plate method. The purpose to choose hot plate method for study of analgesic activity of synthesized compounds is that paws of mice and rats are very sensitive to heat at temperature which does not damage the skin and indicates the central action of title compound. The responses to be observed during study are jumping, withdrawal of the paws and licking of paws, once the test compound was administered orally these responses usually prolonged and compared with control and standard group. The standard drug used is Tramadol at a 20mg/kg dose. The test compounds 2d, 2f, 2h and 2k exhibit very good analgesic activity as comparison against control and standard group. Compounds, 2a, 2b, 2g, 2i and 2j showed moderate analgesic activity where as Compounds, 2c and 2e possess significant activity.

Materials

Microorganisms (Two bacterial strain *E.coli* and *B.subtilis* and two fungi strain *A. niger* and *C. albicans*). Test drug DMSO (dimethylsulfoxide) and distilled water. Standard drug Streptomycin and Amphotericin B.

Discussion

The Thieno [2,3-*d*]pyrimidin-4(3*H*)-one derivatives were successfully prepared by both conventional and microwave irradiation methods.

The title compound were further characterized by physicochemical method and spectral analysis. Melting point was recorded by two different method namely; capillary tube and visible melting point apparatus method and was uncorrected. TLC was done to determine purity by using solvent toluene: ethyle acetate (7:3) and R_f value were reported.

The Infrared spectra for the synthesized compounds were recorded using SHIMADZU - FTIR IRA – Affinity 1 and absorbance peaks were recorded using KBr pellets. This is further supported by NMR studies and Mass studies.

The actual IR, NMR and Mass spectra of the synthesized compounds are given in above figures. The interpretation was carried out by observing the graph.

FTIR spectra of all synthesized compounds showed aromatic C=O stretching vibration peak at 1665.60 cm^{-1} . All derivatives showed a broad absorbance band at about 1490-1580 cm^{-1} associated with stretching vibrations of bonded N-H, indicating present of nitrogen.

Each compound showed a strong absorbance due to presence of C-S at 980-1225 cm^{-1} . All derivatives showed broad absorbance at about 1640-1690 cm^{-1} associated with stretching vibrations of bonded -N=C-, indicating present of nitrogen in the ring. Compound 2d showed a strong absorbance at 1350-1560 cm^{-1} stretching vibration indicating present of C-NO₂ group. Compounds 2e showed absorbance at 1030-1075 cm^{-1} stretching vibration indicating present of Br group.

The structures of synthesized compounds are further confirming by NMR and Mass spectra. ¹HNMR of compounds 2b, 2c and 2h shows a sharp singlet peak at 7-7.5 ppm, indicating presence of Heteroaromatic amine and also

Singlet to multiplet peak at 4-4.7 ppm, indicating presence of s 1H-N. The compound 2b and 2h shows sharp singlet peak at 9-10 ppm, indicating the presence of Aldehydic R-CH=O. The broad multiplet peak in compound 2c at 4.40 ppm, indicating the presence of Aryl-OH. The compound 2b and 2c shows sharp singlet to doublet peak indicating the presence of primary proton at 0.9 ppm and compound 2c shows broad multiplet peak at 1.31 ppm, indicating the presence of secondary proton. The Mass spectra of compound 2b, 2c and 2h shows M⁺ peak at 208, 272 and 278 respectively.

Conclusion

All the compounds prepared herein was screen for analgesic activity by using Eddy's hot plate method. It was observed that compounds 2d, 2k and 2h showed good analgesic activity and compound 2a, 2b, 2g and 2i showed moderate analgesic activity where as other compounds possess less analgesic activity with compared to standard drug Tramadol.

Acknowledgment

The authors are thankful to Principal and Pharmaceutical chemistry department of Priyadarshini J. L. College of Pharmacy Nagpur (Maharashtra) for constant encouragement and providing necessary facilities.

Source of Funding

None.

Conflict of Interest

None.

References

1. Smith HJ. Smith and william's: Introduction to Principle of Drug Design. Great Britain, Anchor Brendon Ltd, 1998:256.
2. Hington L, Mingiyuea Z, Welianng Z, Jiang H. Computational approaches in drug discovery and development of chemical biology; 2008.
3. Kadam SS, Mahadik KR, Bothara KG. Principle of Medicinal Chemistry. Nirali Publication, Fiftineth Edition; 2006:9.
4. Christofferson RE, Marr JJ, Burger's: Chemistry and Drug Discovery. Wiley Interscience Publication, New York, First Edition; 1995.
5. Gupta YK, Gupta M. Post traumatic epilepsy; a review of scientific evidence. *Indian J Physiol Pharmacol.* 2006;50(1):7-10.
6. Hansch C. Comprehensive Medicinal Chemistry. Maxwell Memillan Pergamon Publishing Corporation, Oxford, Fourth Edition; 1990.
7. Chiriffson PH. Practical application of computer aided drug design. Marcel Decker Ink, New-York; 1997.
8. Hosamani KM. In-vivo analgesic and anti-inflammatory activities of newly synthesized benzimidazole derivatives. *European J Med Chem.* 2010;(45):2048-54.
9. Sharma HL, Sharma KK. Principle of Pharmacology. Paras Medical Publisher, First Edition 2008;367-529.
10. Ali A, Mohammad T, Abbas S. Synthesis and Analgesic Activity of N-aryl hydrazone Derivatives of Mefenamic Acid. *J Pharm Pharm Sci.* 2005;8(1):419-25.
11. Limbird E, Molinoff PB, Ruddon RW. Basic of Pharmacology. McGrawhill, New-York, Medicinal Research Review, Seventh Edition 1997, 537.

12. Wolff JH, Baele JM, Wilson and Gisvild: Textbook of Organic Medicinal and Pharmaceutical Chemistry. Eighth Edition 1982;340.
13. KarAshutosh: Medicinal Chemistry. New age international Publisher's, Fifth Revised and Expanded Edition 2010;275.
14. Ibrahim YA and Elwahy AHM: Thienopyrimidines, synthesis, reaction and biological activity. *Advance Heterocyclic Chemistry* 1996;65:235.
15. Ismail KA, Aboulwafa OM, Koreish EA. Synthesis and Antimicrobial Activity of Some tetramethylenethieno [2,3-d]pyrimidine Derivatives. *Farmaco*. 1995;50:611.
16. Hammam AG, Sharaf M and Abdelhafez NA. Synthesis and anticancer activity of pyrimidine and thiazolopyrimidine derivatives using L-ethylpiperidone as a synthon. *Indian J Chem*. 2001;40:213.
17. Aymn ER, Ahmed H, Shamroukh. Synthesis and antimicrobial evaluation of some polycondensedthienopyrimidines derivatives. *Synthesis Comuni*. 2010;40:1149.
18. Rashad AE, Shamroukha AH, Sayed HH. Some novel thienopyrimidine nucleoside analogs, synthesis and in vitro antimicrobial evaluation. *Synthesis community* 2011;41:652.
19. Amr AE, Mohamed AM, Mohamed AF. Synthesis and anticancer activities of new pyridine derivatives fused with nitrobenzosubetron moiety. *Bioorganic Med Chem*. 2006;14:5481.
20. Amr AE, Hegab MI, Ibrahim AA. Synthesis and reaction of some fused oxazizone, pyrimidanone, thienopyrimidanone and triazinone derivatives with thiophene ring as analgesic' anticonvulsant and anti-parkinsons agent. *Monatch Chem*. 2003;135:1395.
21. Hassan NA, Hegab MI, Rashad AE. Synthesis and antimicrobial activity of some cyclic and acyclic nucleosides of thieno[2,3-d]pyrimidines. *Nucleosides, Nucleotides* 2007;26:379.
22. Elmahd KM, Elkazak AM, Abdel Megid MM. Synthesis, characterization and biological evaluation of Some new Thieno[2,3-d]pyrimidine derivatives. *J Adv Chem*. 2013;5:581.
23. Rashad AE, Ali MA: Synthesis and antiviral screening of some thieno[2,3-d]pyrimidine nucleosides. *Nucleosides, Nucleotides*. 2006;25:17.
24. Abdel Megid M, Elmahdy KM, Rashad AE. Synthesis and applications of pyrimidinethiones. *Glob J Sci Res*. 2013;13:7.
25. Shamrouth AH, Rashad FE, et al: The chemistry of pyrazolopyrimidines and their applications. *Org Chem AI J*. 2004;10:224.
26. Abdel Megid M, Elkazak AM. Synthesis of furopyrimidine derivatives. *J Adv Chem*. 2013;3:229.
27. Litvinov VD. Thienopyrimidines, synthesis, properties and biological activity. *Russian Chemical Bulletin, International Edition*; 2000;53:487.
28. Dipen KS, Kantilal RV. POCl₃ Catalyzed, one step solvent free Synthesis of some novel thieno[2,3-d]pyrimidin-4(3H)one derivatives as antimicrobial agents. *J Souidi Chem Soc*. 2018;22(2):248-53.
29. Shachindra LN, Murugan V. Synthesis and evaluation of substituted thieno[2,3-d]pyrimidin-4-yl amines for antimicrobial activity. *Ultra Sci*. 2015;27(3):195-202.
30. Bakavoli M, Begherzadeh G, Vaseghifar M. Iodine catalysed synthesis and antimicrobial evaluation of thieno[2,3-d]pyrimidine derivatives. *J Chem Res*. 2009;3:653-5.
31. Kappe CO: Controlled microwave heating in modern organic synthesis. *Angewandte Chemie*. 2004;43(49):6250-80.
32. Vogel A. Book of elementary practical organic chemistry part-2. LongmerSingapore Publisher, second edition, Pvt Ltd, 2001;324-47.
33. Stahl E. Thin layer chromatography. Academic press. New York, Second edition, 1969;904.
34. Pavia D, Lampman G, Kriz G, Vyvyan J. Introduction to spectroscopy. Cengage learning, Sixth edition. 2007;401-500.
35. Furniss B, Hannaford A, Smith W, Tatchell. Vogel's textbook of practical organic chemistry, fifth edition, London. 1996;1032-4.
36. Silverstein RM. Spectrometric identification of organic compounds. John Wiley and sons Inc, sixth edition 2015;2:143.
37. OECD: Guideline, 423, Acute oral toxicity. Environmental Health and Safety Monograph Series on testing and assessment No 24. 2004.
38. Vogel HG, Sandow J. Drug Discovery and Evaluation, Pharmacological Assays. Third edition, 1013-4.
39. Arula N. Study of analgesic effect of septicin in comparison with aspirin and tramadol in experimentally induced pain in rats. *Int J Basic Clin Pharmacol*. 2003;10: 2271-5.
40. Gupta JK, Sharma PK. Synthesis and analgesic activity of novel pyrimidine derivatives of coumarin moiety. *Acta Poloniae Pharmaceutica- Drug Res*. 2011;68(5):785-93.
41. Zienab MN. Synthesis of new pyrimidine derivatives with evaluation of their anti-inflammatory and analgesic activities. *ActaPoloniaePharmaceutica- Drug Res*. 2011;68(4):507-11.
42. Abdel Rohman BA, Hoda AR. Synthesis and biological evaluation of thieno[2,3-d]pyrimidine derivatives for anti-inflammatory, analgesic and ulcerogenic activity. *Acta Pharm*. 2007;57:395-411.
43. Wagnat W. Screening for antidepressant, sedative and analgesic activities of novel thiophene derivatives. *Acta Pharm*. 2008;58:1-14.
44. Algarsamy V, Rajasolomon V. Design and synthesis of 2-methylthio-3-substituted-5,6-dimethylthieno[2,3-d]pyrimidine-4(3H)-ones as analgesic, anti-inflammatory and antibacterial agents. *Med Chem*. 2007;3:67-73.
45. Kokare C: Pharmaceutical microbiology, principle and applications. Nirali publication, Ninth edition; 2013;12-7.
46. Kale V, Bhusari K. Applied Microbiology. Himalaya publishing house, third edition; 2015;128.

How to cite: Kawade DP, Chaple DR, Khedekar PB. Synthesis, physicochemical characterization and analgesic evaluation of some new thieno [2,3-D] Pyrimidin 4(3H) one derivatives. *Int J Pharm Chem Anal*. 2020;7(1):32-8.