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Review Article

Biological Diversity of Thiophene: A Review

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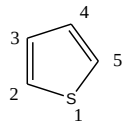
ABSTRACT

Thiophene has been established as the potential entity in the largely growing chemical world of heterocyclic compounds possessing promising pharmacological characteristics. A series of thiophene compounds can be synthesized through various synthetic routes, with diverse pharmacological activities. In future the moiety & its derivatives draw a special attention of medicinal chemists to produce various scaffolds with potent biological activities & also as a lead pharmacophore of any compounds & for clinical investigations. This review provides various synthetic strategies of thiophene analogues.

Keywords: Thiophene, Isatin(1H-indole-2,3-Dione), Gewald reaction, Volhard-Erdmann cyclization, azuleno[1,2-c] thiophene.

1. INTRODUCTION

Thiophene, containing a sulfur atom at 1 position, positions 2 and 5 are equivalent in the parent ring, as are the 3 and 4 positions. It is a heterocylic, aromatic compound with formula C_4H_4S, chemical name is thiacyclopentadiene. Thiophene is taken from the Greek word *theion* means sulfur and *phaino* means shinning. Consisting of a flat five membered ring, it is aromatic as indicated by its extensive substitution reactions.



thiophene

Thiophene was discovered as a contaminant in benzene [1], detected by the *Indophenin reaction*. It was observed that Isatin (1H-indole-2,3-Dione) forms a blue dye (indophenin) when mixed with sulphuric acid and crude benzene, was believed to be react with benzene. Victor Meyer was able to isolate this new heterocyclic compound responsible for this reaction was thiophene [2].

Gewald reaction [3], Volhard-Erdmann cyclization [4], Paal thiophene synthesis [5], Paal-Knorr Synthesis [6], Hinsberg Synthesis [7], Fiessel-mann Thiophene Synthesis [8], are the common methods for the preparation of thiophene nucleus. Synthetically thiophene prepared from thioacetamides [9], thiocarbonyl [10] compounds. Commercially thiophene manufactured by reaction of n-butane, sodium succinate with sulfer vapour & phosphorus trisulfide respectively [11]. Thiophene and its derivatives occur in petroleum /coal tar.

At room temperature, thiophene is a toxic, flammable and aromatic colourless liquid with a mildly pleasant odor reminiscent of benzene [12]. The molecular mass of thiophene is 84.14 g/mol, density is 1.051 g/ml and Melting Point is -38 °C. It is insoluble in water but soluble in most organic solvents including alcohol and ether. The "electron pairs" on sulfur are significantly delocalized in the π electron system [13], due to this it behaves extremely reactive benzene derivative. Like benzene, thiophene forms an *azeotrope* [14] with ethanol. The similarity between the physicochemical properties of benzene and thiophene is striking. For example, the boiling point of benzene is 81.1°C and the one of thiophene is 84.4°C (at 760mm Hg) and therefore, thiophene and benzene are a well known example of *bioisosterism* [15]. It can be easily sulfonated, nitrated, halogenated, acylated. It cannot be alkylated & oxidized [16].

Thiophenes are important heterocyclic compounds, are widely used as building blocks in many agrochemicals [17]. Thiophene possesses antimicrobial [18], analgesic and anti-inflammatory [19], antihypertensive [20], diabetes mellitus [21], Gonadotropin Releasing Hormone antagonist [22], cholesterol inhibition activity [23], antiallergic [24], antitumor [25] activities.

A brief account is given below:

2. ANTIMICROBIAL ACTIVITY

Antimicrobial drugs are effective in the treatment of infection because of their selective toxicity; that is, they have the ability to injure or kill an invading microorganism without harming the host [26]. It is evident from literature that thiophene derivatives are known to be associated with broad

spectrum of biological activity like antibacterial, antifungal. Benzo thieno[3,2-e]triazolo, thieno-pyrimidines, s-triazine incorporated thiophene derivatives thiadiazine analogues, imidazolines and thiourea derivatives possess antimicrobial agent and it act against variety of gram-positive and gram-negative bacterias, some fungi and viruses.

3. PHOSPHODIESTERASETYPE IV INHIBITORS (PDE4)

In the past years, attention has been primarily focused on cyclic nucleotide phosphodiesterase IV (PDE4) as a suitable target for anti-inflammatory therapy in respiratory diseases. The mixed anti-inflammatory and bronchodilatory profile of PDE4 inhibitors could allow the discovery of new agents, steroid-sparing compounds with utility in diseases associated with chronic airway inflammation, particularly in themanagement of asthma and COPD [37].

PDE4 isoenzymes (PDE4A-D) are encoded by 4 genes and more than 20 splice variants providing the basis for the continued interest in developing selective PDE4 inhibitors for a number of inflammatory diseases. At the present time there are seven known PDE isoenzyme families (PDE1-7) [38]. Aminothiophenes, isoquinoline analogues of thiophene are reported as PDE-4 agents.

4. CYTOTOXICITY

Cancer is a disease characterized by uncontrolled multiplication and spread of abnormal forms of the body's own cells [41]. From literature survey it is well known that thiophene heterocyclic exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent. Analogues of Triazolo[4,3-a]pyrimidin-6-sulfonamide with an incorporated thiazolidinone moiety, Thieno[2,3-*d*]pyrimidine derivatives, 2,4-Diamino thieno[2,3-*d*]pyrimidines, imidazo [4',5:4,5]thieno[3,2-*d*]pyrimidine analogues possess cytotoxicity activity.

5. CNS DEPRESSANT ACTIVITY

Depression is defined as disorders of mood rather than disturbances of thought or cognition. Depression accompanied by hallucination and delusion [41]. Some of thiophene derivatives show CNS depressant activity. Substitutedthieno[2,3-d]pyrimidine analogues, piperazinyl , benzodiazepine analogues of thiophene and thiophene fused quinazolines shows antipsychotic, neuroleptic & anticonvulsant activity.

6. ANALGESIC AND ANTI-INFLAMMATORY

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbial agents [26]. It inhibits Prostaglandin synthesis at the site of injury [51]. Analgesic drug is used to control the pain. Prostaglandin E_2 (PGE_2) is thought to sensitize nerve ending to the action of bradykinin, histamine and other chemical mediators released locally by the inflammation process [26]. Thieno[2,3-*d*]pyrimidin- 4(*3H*)-ones, thiophene based thiazine, benzo-thiophene derivatives possess analgesic and anti-inflammatory activity. The anti-inflammatory activity was studied by Carrageenan induced paw oedema method and anaglesic activity studied by tail flick and hot plate method.

7. MISCELLANEOUS ACTIVITY

Thiophenes and their derivatives show many activites which are discussed above, some more activities are mentioned in table.

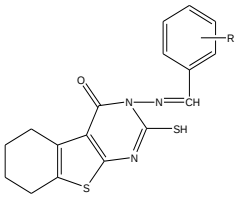
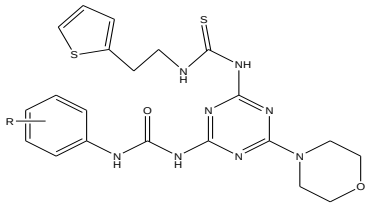
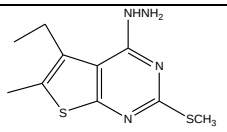
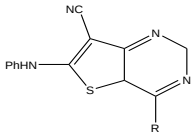
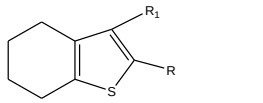
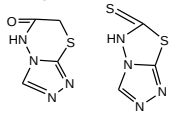
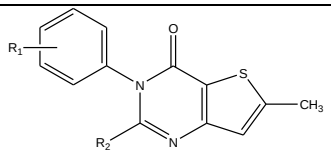
8. CONCLUSION

The informational data, available in literature so far, rendered thiophene, a significantly important class of heterocycle and their applications are challenging in chemotherapy of various infections etc. A survey of thiophene revealed the moiety have attracted a great deal of interest of medicinal chemist and biochemist and rendered as a lead molecule for designing potential bioactive agents. Also, its derivatives are reported including broad-spectrum pharmacological activities.

This review accompanying supplementary information & its references would extend great deal of help to researchers in determining the best and most productive, economical, suggestive and clinically important compounds of thiophene. Further we can conclude that many other derivatives of thiophene can be synthesized which will be expected to show potent pharmacological activities.

9. ACKNOWLEDGEMENT

The authors are thankful to librarians of various Institutes & libraries NISCAIR New Delhi and to the Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad for providing literature survey facility to carry out the project work.

S. No.	Scientist Name	Synthesized compound	Structure	Biological Activity
1.	Kavitha P.N.et al. [27]	3- (*substituted*) amino-2-mercapto-5,6,7, 8-tetrahydro benzo (b)thieno [2,3-d] pyrimidin-4(3H)-one analogues.	 R= 2-OH, 2-NO_2, 4-OCH_3, 2-Cl, 4-Cl, 2,3,4-triNO_2	Antimicrobial activity, against *B.subtilus, K.pneumonia* and *A.niger,* compared with standard drugs Ampicillin and Miconazole.
2.	Desai Akshay et al. [28]	2-thiophene-2-ethylthioureido-4-morpholino-6-(*aryl)* ureido-s-triazine derivatives.	 R= 2-NO_2, 3-Cl, 4-Cl, 4-CH_3, 4-NO_2, 2-CH_3	Antimicrobial activity, against *S.typhi, C.albicans,* compared with standard drug Tetracycline.
3.	Bhuiyan Md. Mosharef Hossain et al. [29]	4-hydrazino-2-mehylthio-5-ethyl-6-methylthieno [2,3-d] pyrimidine.		Antimicrobial activity, against *B.cereus, V.chol-erae, A.alternate,* compared with standard drugs Ampicillin and Nystatin.
4.	El-Saghier Ahmed M. M. et al. [30]	4-(*substituted*)-7-cyano-6-phenyl aminothieno [3,2-d] pyrimidin analogues.	 R = 4-BrC_6H_4 , CH_3	Antimicrobial activity. Good activity against B.subtilis and *St.aureus,* compared with reference drug Amoxicillin.
5.	Shiradkar M. et al.[31]	N-[3-(*substituted*)-7H-[1,2,4] triazolo [3,4-b] [1,3,4] thiadiazine / thiadiazol-4,5,6,7-tetrahydrobenzo[b] thiophene.	 R = $NHCOCH_3$ R_1 = 	Good Antimicrobial activity against *E.coli, S.aureus, A.nigar,* compared with standard drugs Gentamycin and Nystatin.
6.	Chander Mohan et al. [32]	6-methyl-2-phenyl -3-(*substituted*)-3H-thieno[3,2-d] pyrimidin-4-one derivatives.	 R_1 / R_2: *o*-CH_3 Ph; p-CH_3 SMe; p-Cl SMe; p-Cl Ph	Antimicrobial activity, against *B. subtilis, E.coli, P.aeruginosa* compared with standard drug Ciprofloxacin.

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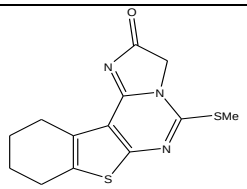
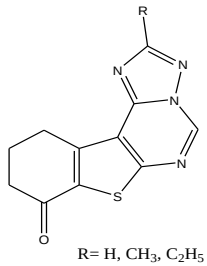
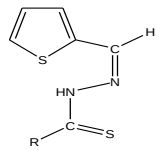
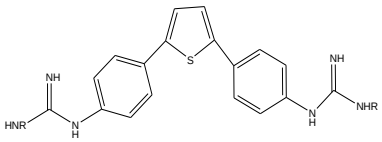
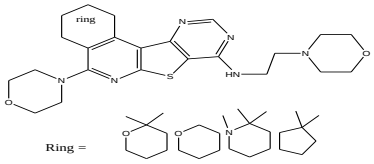
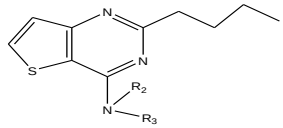
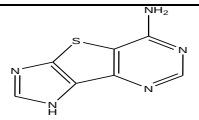
7.	Bhuiyan Md. Mosharef Hossain et al. [33]	thieno[3,2-e] imidazo[1,2-c] pyrimidin-2(3H)one derivative.		Antimicrobial activity, compare to reference drugs Ampicillin with Nystatin, against *B. cereus, S.typhi* and *A.alternata*.
8.	S. Shetty Nitin kumar et al. [34]	(*Substituted*) 8,9,10,11-tetra hydro[1]benzo thieno[3,2-e] [1,2,4]triazolo [1,5-c]pyrimidine -8-one analogues.	 R= H, CH_3, C_2H_5	Good Antibacterial activity against *B. subtilis* comparable to the standard drug Ampicilin.
9.	Sangita Sharma et al. [35]	thiophene-2-carboxaldehyde-(*substituted)*thiosemi-carbazones.	 R = $NHCH_2CH_2CH_3$, $NHCH_2CH_2CH_2CH_3$,	Antiamoebic activity against *E. histolytica*.
10.	Gonzalez Jose L. et al. [36]	(*Substituted*) bis-2,5-[4-guanidino phenyl] thiophenes.	 R = H , CH_3 , Ph , p-tolyl , c-hexyl	Antiparasitic activity against *T. brucei rhodesiense*, *P. falciparum*, *L. donovani and T. cruzi* parasites.
11.	TaltavullJoan et al. [39]	(*Substituted*)1,2, 3,4-tetrahydro pyrimido thieno[2,3-c] iso quinoline-8-amino (2-morpholin-4-yl ethyl) analogues.	 Ring =	Phosphodiesterase IV inhibitors (PDE4), a target for the treatment of asthma and chronic obstructive pulmonary disease (COPD).
12.	Crespo Maria I. et al. [40]	2-Butyl-4-(*substituted*) aminothieno [3,2-*d*] pyrimidine.	 R_2 Cyclohexyl Benzyl R_3 H Methyl	Type 4 Phosphodiesterase Inhibitors with respect to standard drug Rolipram.
13.	Seley L. Katherine et al. [42]	6-Aminoimidazo [4',5' :4,5] thieno [3,2-*d*] pyrimidine.		More potent Anticancer agent then other thieno compounds.

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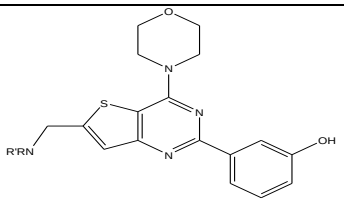
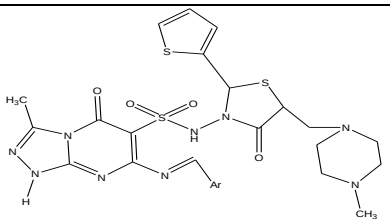
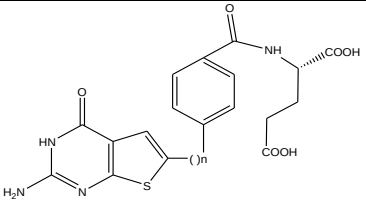
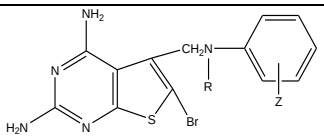
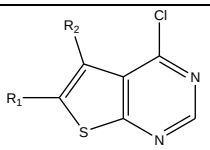
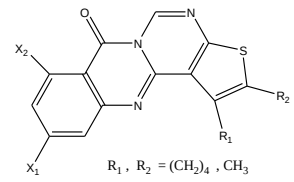
14.	Folkes Adrian J. et al. [43]	(*Substituted*) 4-morpholin-4-yl-thieno[3,2-*d*] pyrimidine analogues.	 R, R' = N-methyl piperazine, Me_2NCH_2	Anticancer agent. Potent inhibition of cancer cell proliferation as well as in vivo absorption and tumor exposure.
15.	Hafez H. N. et al. [44]	*(Aryl substituted)* 3-methyltriazolo [4,3-a] pyrimidin -6-sulfono-2-thieno[(4-methyl piperazine)] analogues.	 Ar = 4-$CH_3OC_6H_4$, 2-$CH_3C_6H_4$, C_6H_4	Anticancer activity. Inhibited the growth of cancer cell lines, showing a good selectivity on leukemia penal.
16.	Deng Yijun et al. [45]	2-amino-4-oxo- 6 -*(substituted)* thieno[2,3-*d*] pyrimidines with bridge length (from 2 to 8 carbon atoms)	 n = 2-8	Antitumor activity.
17.	Roso-wsky Andre et al. [46]	2,4-Diamino-5-[(*substituted*) methyl]-6-bromo thieno[2,3-*d*] pyrimidine analogues.	 R = H, Me, H Z = 3,4,5-$(OMe)_3$, 3,4,5-$(OMe)_3$, 3,5-Cl_2-4-[1-pyrrolo]	Antifolates, as Inhibitors of *Pneumocystis carinii* and *Toxoplasma gondii* Dihydrofolate Reductase.
18.	Sharma Chanchal et al. [47]	4-chloro-5,6-*(disubstituted)* thieno [2,3-d] pyrimidine analogues.	 R_1 = CH_3, C_2H_5 R_2 = H	Significant Antipsychotic activity, with reference drug Olanzapine.
19.	Laddha Sachin S. et al. [48]	*(Substituted)*-1,2,9,11-tetrahydro-7H-thieno[2',3':4,5] pyrimido [6,1-b]-quinazolin-7-one.	 R_1 , R_2 = $(CH_2)_4$, CH_3 X_1 , X_2 = H , H	Potent Anticonvulsant activity, compare with standard drugs Phenytoin / Phenobarbital.

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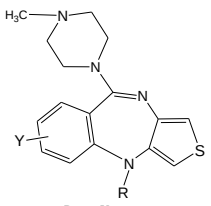
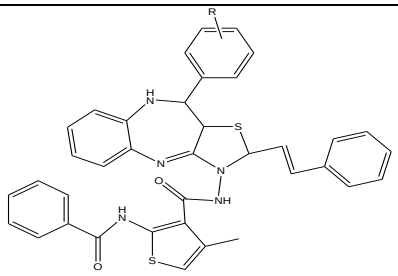
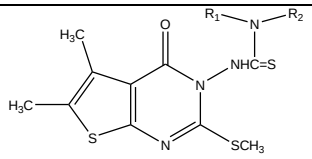
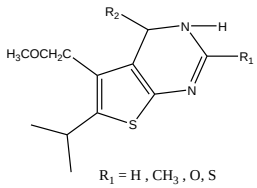
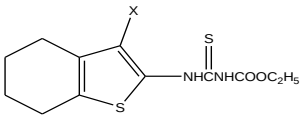
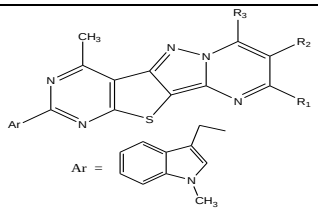
20.	Press Jeffery B. et al. [49]	(*Substituted)*9-(4-Methyl-l-piperazinyl)-4H-thieno[3,4-b][1,4] benzodiazepines.	 R Y a = H CH_3 b = 7-Cl H c = 7-F CH_3 d = 7-F H	Potential CNS Agents as neuroleptic , antidepressant agents.
21.	Ghogare J.G. et al. [50]	(*Substituted*)9H, 10H, 3-[N- 4 methyl-2-benz amidothiophen 3-yl-carbonyl amino [2-(2'-phenyl 1'-ethylenyl)] 10-(*aryl*) thiazolidino [4, 5-b] 1,5- benzodiazepines.	 R = 2-OH , 2-Cl, 3-NO_2 , 4-F	Potential anticonvulsant agents.
22.	Alagarsamy V. et al.[52] (2007)	2-Methylthio-3-(*substituted*)-5,6-dimethylthieno [2,3-*d*] pyrimidin-4(*3H*)-ones.	 $R_1 = (CH_3CH_2)_2N$, pyroolindinyl $R_2 = (CH_3CH_2)_2N$, pyroolindinyl	Analgesic agent, compared with standard drug diclofenac.
23.	Abdal Rehman. B. A. El-Gazzar et al. [53]	(*substituted*)- 6-isopropyl-3H-thieno[2,3-d] pyrimidine analogues.	 R_1 = H , CH_3 , O, S R_2 = =O , NH_2	Anti-inflammatory and analgesic activity, showed good result as compare to standard drug Acetylsalicylic acid.
24.	Wardakhan W. W. et al. [54]	3-(*substituted*) -2-(N-ethoxy carbonyl thiouryl) 4,5,6,7-tetrahydro benzo[b]thiophens.	 X = CN, $COOC_2H_5$	Antidepressant and Analgesic activity, comparable to reference drug Indomethacin.
25.	Amr Abd El-Galil E. et al. [55]	(*substituted*)-Pyrimido pyrazolothieno [2,3-d] pyrimidine derivatives.	 Ar = R_1 R_2 R_3 a= Ph H NH_2 b = H H Ph c = Ph CN NH_2	Anti- inflammatory and analgesic activity, compare to reference drugs Prednisolone and Veldecoxib.

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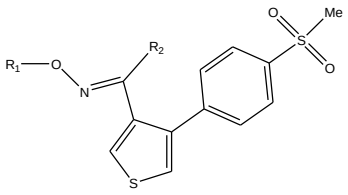
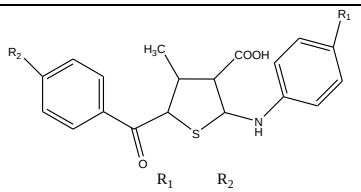
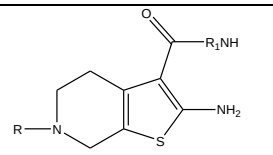
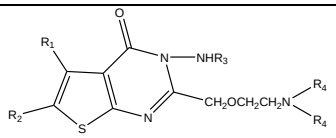
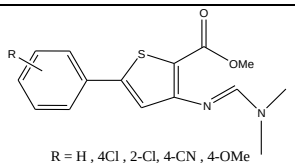
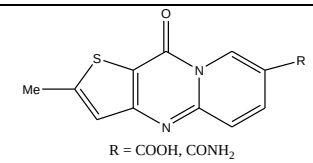
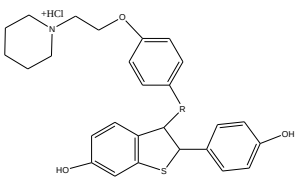
26.	Balsamo Aldo et al.[56]	(*substituted*)(2-aryl-1-thiophene-1-alkylidene)-(arylmethyloxy) amine analogues.	 R_1 R_2 a = $PhCH_2$ H b = $(3,4\text{-}OCH_2O)C_6H_3CH_2$ H c = $PhCH_2$ Me d = $(3,4\text{-}OCH_2O)C_6H_3CH_2$ Me	Anti-inflammatory and COX-2 inhibitors.
27.	Molvi Khurshid I. et al. [57]	2-(*substituted*)-5-(4-methoxy benzoyl)-4-methylthiophene-3-carboxylic acid derivatives.	 R_1 R_2 a = H OCH_3 b = CH_3 OCH_3 c = OCH_3 OCH_3 d = F OCH_3 e = Cl CH_3	Anti- inflammatory and analgesic activity, compare with standard drug Ibuprofen.
28.	Aurelio Luigi et al. [58]	3-and 6-(*Substituted*) 2-amino-4,5,6,7-tetrahydrothieno [2,3-c]pyridine derivatives.	 R = Me R_1= CONHBn, $CONHNH_2$, CONHNHPh	Adenosine receptor allosteric modulators and antagonists.
29.	Shireesha B. et al. [59]	2-N,N (*disubstituted*) aminoethoxy methylthieno [2,3-*d*]-pyrimidin-4(3*H*) one derivatives.	 R_1,R_2 R_2 R_3 a = $(CH_4)_2$ H CH_3 b = $(CH_4)_2$ H C_2H_5 c = $(CH_4)_2$ C_6H_5 CH_3 d = $(CH_4)_2$ C_6H_5 C_2H_5	Antihistaminic and anticholinergic activity, compare with standard drug Chlorpheniramine maleate.
30.	Tavares Francis X. et al. [60]	(*substituted*) Methyl-3-(dimethylamino) methylidene amino-5-phenyl -2-thiophene carboxylate analogues.	 R = H , 4Cl , 2-Cl, 4-CN , 4-OMe	Antagonists of Melanin-Concentrating Hormone (MCH) receptor 1.
31.	David T. Connor et al. [61]	7-(*substituted*) 10-oxo-10H-pyrido[1,2-a] thieno[3,2-d] pyrimidine derivatives.	 R = COOH, $CONH_2$	Antiallergic Activity.
32.	Palko-witz Alan D. et al.[62]	(*substituted*) [2-(4-Hydroxy phenyl)-6-hydroxybenzo[*b*] thieno-3-yl][4-[2-(1-piperidinyl) ethoxy]phenyl] hydrochloride.	 R = CO , CH_2 , S , O , NH	Highly Potent, Selective Estrogen Receptor Modulator.

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