

REVIEW ARTICLE

Tri- and Tetra- Cyclic Theophylline Derivatives as a Potential Agents Acting on CNS and CVS: An Overview

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ABSTRACT

Most all tricyclic compounds derived from theophylline were investigated in the respect of their anticancer, circulatory blood system activity and as anti-inflammatory agents. The synthesis of new tricyclic purine derivatives with anellated in 7,8-position of theophylline five, six, seven membered heterocyclic ring system. of lactam and non-lactam structure modified by a basic substituent at N8, N9 and N10 position. It has been shown that new tricyclic theophylline derivatives possess sedative, analgesic properties, neuroleptic-like activity and hypothermizing properties. Some structural elements modification influence the central nervous system activity in the respect of:

- Kind of the additional ring.
- Alkylamine substituent in 9 position of tricyclic system.

Our goal was to give a wide scope literature review of the tricyclic and tetracyclic theophylline derivatives as adenosine, 5-HT, benzodiazpine receptors, and phosphodiesterase inhibitors, because the new compounds are of interest due to their potential pharmacological activities, and they will be useful as standard compounds for treatment of central nervous system as (hypnotic, sedative, hypothermizing properties, anti-epileptic effects and analeptics –like properties), and cardio-vascular system disorders as (anti-hypertensive, anti-arrhythmia activities).

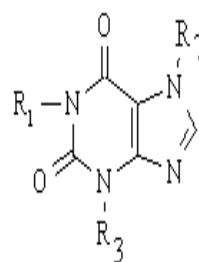
**Key words:** Xanthine; tricyclic & tetracyclic theophylline derivatives; CVS & CNS activity of fused [2,1-f] theophyllines.

INTRODUCTION

Overview of methylxanthine derivatives used in therapy.

At least half of the population of the world uses tea-containing methylxanthine: caffeine, small amount of theophylline and theobromine, prepared from the leaves of *Thea sinensis*. First half of the last century confirmed that methylxanthines share many pharmacological actions and differ only in potency. They are CNS stimulants predominantly caffeine, while theophylline has some CNS-stimulant properties, and theobromine possess only weak stimulant activity<sup>[1]</sup>.

All these well known drugs are xanthines (2,6-dioxypurine) derivatives, easily chemically transformed to uric acid (2,6,8-trioxopurine). Theophylline is 1,3-dimethyl xanthine, theobromine 3,7-dimethylxanthine and caffeine 1,3,7-trimethyl xanthine respectively<sup>[2]</sup>.



$R_1 = R_3 = \text{CH}_3, R_7 = \text{H}$  Theophylline

$R_1 = R_3 = R_7 = \text{CH}_3$  Caffeine

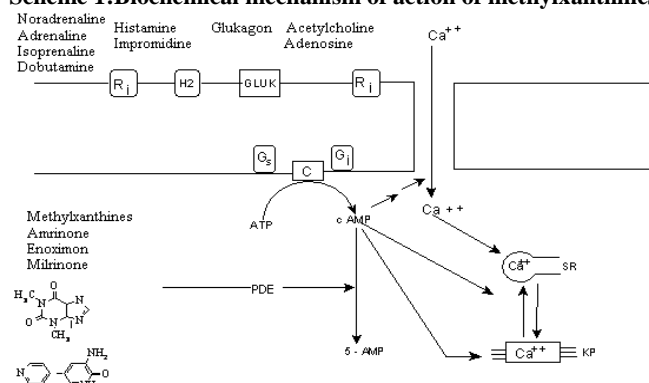
$R_3 = R_7 = \text{CH}_3, R_1 = \text{H}$  Theobromine

Biochemical mechanism of action of methylxanthines :

The naturally occurring methylxanthine, Caffeine and Theophylline are the classical adenosine receptor antagonists. Caffeine is widely consumed in beverages, theophylline is used as a drug in the treatment of bronchial asthma and several other xanthines derived from caffeine and theophylline are therapeutically used as analeptics, antiasthmatics, vasodilators, antihypertensive and diuretics. Besides adenosine receptor antagonistic activities, other mechanism of action including inhibition of phosphodiesterases (PDE), Mobilization of the intracellular calcium ions

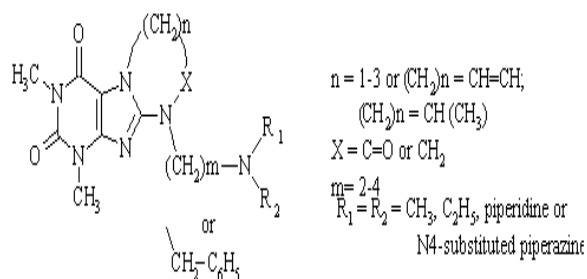
(Ca<sup>2+</sup>) via cell membrane hyperpolarization also play a significant role in their biological activity [2]. Inhibition of enzyme-phosphodiesterase leads to an increase of lipolysis and glycogenolysis as a result of elevated concentration of c AMP [3]. Inhibition of cyclic nucleotide phosphodiesterase causes accumulation of c-AMP, however an increase of intracellular c-AMP concentration may influence the movement of Ca<sup>2+</sup> which is involved in smooth muscle contraction with the result that relaxation occurs. Theophylline stimulates the release of catecholamines from the adrenal medulla and also inhibits the enzyme catecholamine-O-methyl transferase (COMT) which contribute to it's bronchodilatory effects [1-3]. Some of bis-pyridyl -derivatives (Amrinone) exhibits the similar profile of PDE inhibition [3-5].

**Scheme 1: Biochemical mechanism of action of methylxanthines**



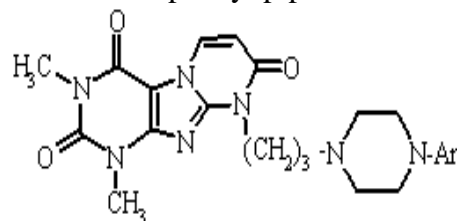
**Tri- and tetra- cyclic fused theophyllines and their analogs:**

Extensive studies have been performed on the fused tri- and tetra-cyclic systems derived from theophylline including synthetic procedures and structure determination. Only few of the synthesized compounds in the group of tricyclic theophylline derivatives were pharmacologically tested. Recently, it was found that anellation of five-, six- or seven- membered ring at 7,8-position of theophylline changed the profile of its CNS activity. The Pharmacological evaluation of the series of novel tricyclic theophylline derivatives with fused third ring, generally demonstrated their sedative effects on CNS. Pyrimido or diazepino [2,1-f] theophylline possessing basic substituents (e.g piperazinopropyl, dimethylaminopropyl, piperidinopropyl) revealed marked depressant effects on CNS [6-12].



N8-Phenylpiperazinopropyl-1, 3, 6, 7-tetrahydro-(8H)-imidazo [2, 1-f] theophylline showed significant antiserotonin and long-lasting hypothermizing effects, whereas N8-benzyl-1, 3, 6, 8-tetrahydroimidazol-7-on-[2,1-f]-theophylline possessed antiseizure properties [13,14].

Lactam and non-lactam tricyclic theophylline derivatives with phenylpiperazino-alkyl substituent containing terminal pyrimidopurine or 1,3-diazepinopurine demonstrating high affinity as 5-HT<sub>1A</sub> /5-HT<sub>2A</sub> receptor ligands have been developed [15]. The structural modifications of pyrimido[2,1-f]purines and diazepino[2,1-f]purines with 1-(chlorophenyl)-and 1-(3-methoxy-phenyl)piperazine gave the compounds with affinity on 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors (K<sub>i</sub>: 2,8-43 nM) depending on the structure of 1-arylpiperazine moiety and the cyclic amide fragment. The most potent were arylpiperazino-alkyl derivatives of C6-C7 unsubstituted tricyclic pyrimidino-8-on [2,1-f]theophylline. Generally, methoxyphenyl substituted derivatives were more active at 5-HT<sub>1A</sub> receptor site than their analogs with m-chloro-phenyl piperazine [14].



Ar = phenyl, m-chlorophenyl, o-methoxyphenyl

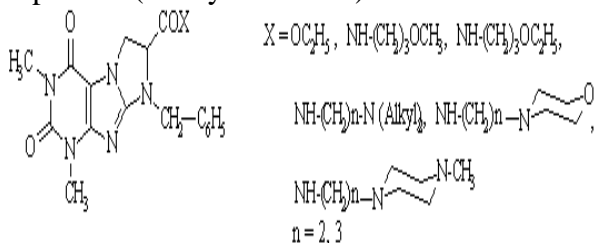
Higher homolog of the above-described tricyclic derivatives, containing 1,3-diazepine ring in the position 7,8 of theophylline were also developed [16, 17]. The diazepino [2,1-f] theophyllines were interesting, because of their high CNS *in vivo* activity probably related to the incorporation of the seven-membered ring, high lipophilicity and better penetration to the central nervous system [16]. The enlargement of the third fused ring and elongation of the alkyl spacer causes loss of affinity to the 5-HT<sub>1A</sub> receptors in comparison with pyrimidin-8-on[2,1-f]theophylline derived analogs [18].

The influence of tricyclic imidazo-, pyrimido-, and diazepino-[2,1-f] theophyllines on CNS is mainly related to the kind of additional ring fused in 7,8-position of theophylline, but also depends on the structure of alkylamino substituent in N9-position of tricyclic system [15]. The replacement of the methylene group with a carbonyl one in pyrimido [2,1-f] theophyllines or diazepino [2,1-f] theophyllines (lactam structure)

did not lead to a significant influence on the direction of the pharmacological activity<sup>[15]</sup>. Length reduction of alkylene chain between dialkylamino substituent and tricyclic system from three or four to two carbon atoms resulted mostly in an increase of toxicity<sup>[16]</sup>.

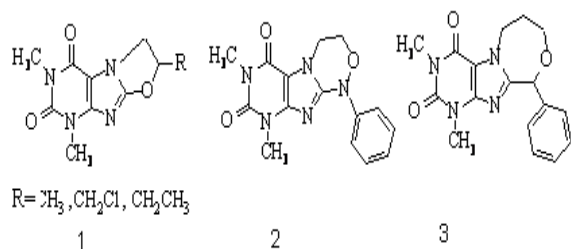
Some phenylpiperazine alkyl derivatives of tricyclic systems evaluated for their affinities of 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors were classified as postsynaptic antagonists or partial agonists of 5-HT<sub>1A</sub> receptors. The replacement of the phenylpiperazinoalkyl substituent with the pyrimidinylpiperazino alkyl side chain generally decreased the activity and revealed some neurotoxic effects. Also definitely changed the profile of the activity on 5-HT<sub>1A</sub> receptors from antagonism to agonism<sup>[16,17]</sup>.

Some new imidazo[2,1-f]theophylline derivatives with carboxylic function substituted in fused third ring (prolino-theophylline), modified by ester and different amide showed the stimulating effects on CNS demonstrated as an increase in locomotors activity of animals there by revealing similar profile of pharmacological activity to parent compounds (methylxanthines)<sup>[17]</sup>.

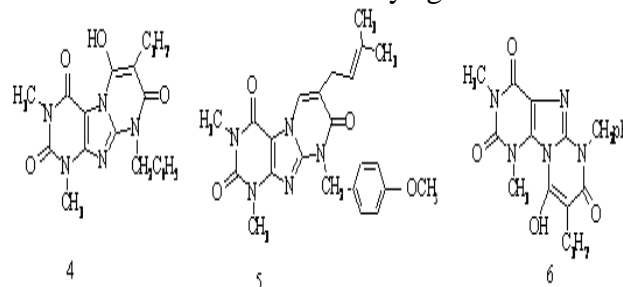


Among a number of the investigated derivatives with different tricyclic structures, pyrimidin-8-on[2,1-f]theophylline with a double bond between C6-C7 and internal carbonyl group in the third ring seems to be the most interesting as CNS pharmacophore. On the other, hand many of centrally active drugs possess the carboxylic function, often modified by ester or amide. Some of them like valproic acid<sup>[3]</sup> and valpromide<sup>[4]</sup> act as antiepileptics, while amineptine<sup>[5]</sup> and tianeptine<sup>[6]</sup> are potent antidepressant agents.

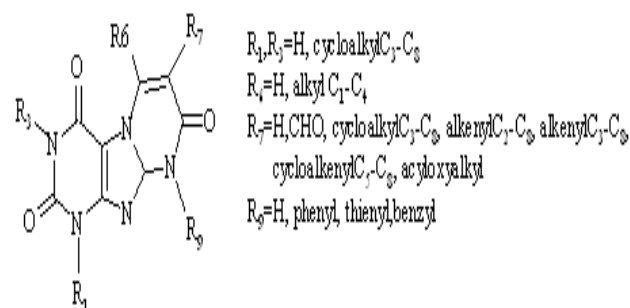
Tricyclic theophyllines with anellated oxazole 1, oxazine 2, and oxazepine 3 were pharmacologically evaluated *in vivo* antiepileptic tests and *in vitro* for their affinity to adenosine receptors<sup>[18]</sup>.



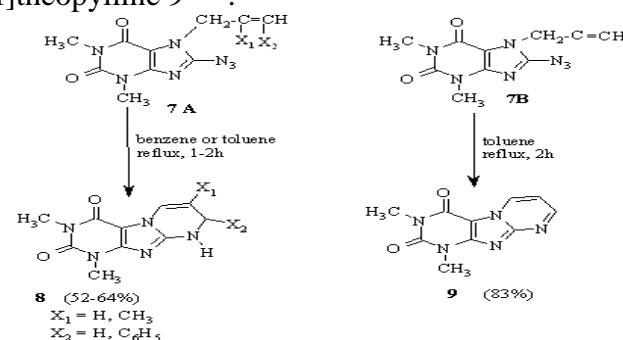
Some of tricyclic pyrimido[2,1-f] and pyrimido[2,1-g]theophylline derivatives **4-6** possess an anti-inflammatory properties. The compounds described represent a novel class of non-steroidal anti-inflammatory agents<sup>[18]</sup>.



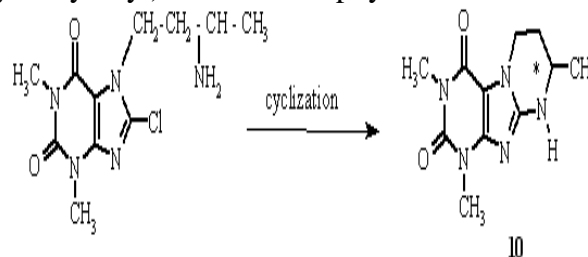
Some of the compounds from this group were converted by reduction in 2-position to appropriate 2-deoxypyrimido [2,1-f] purine-4,8-(1H, 3H, 9H)-dione derivatives [21] and investigated in the treatment of hyperproliferative skin disease<sup>[22]</sup>.



A great many compounds derived from theophylline were chemically synthesized but not examined pharmacologically. Cycloaddition of 7-(2-alkenyl)-8-azidotheophyllines **7A**, **7B** yielded 7,8-disubstituted dihydropyrimido[2,1-f]theophylline **8** and appropriate pyrimido[2,1-f]theophylline **9**<sup>[23]</sup>.

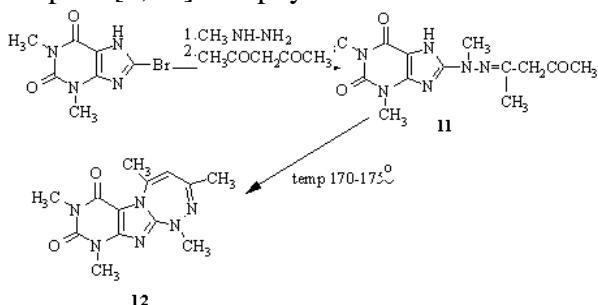


Pyrimido[2,1-f]theophylline derivative **10** was obtained via reductive cyclization of 7-(3-hydroxybutyl)-8-chlorotheophylline<sup>[24]</sup>.



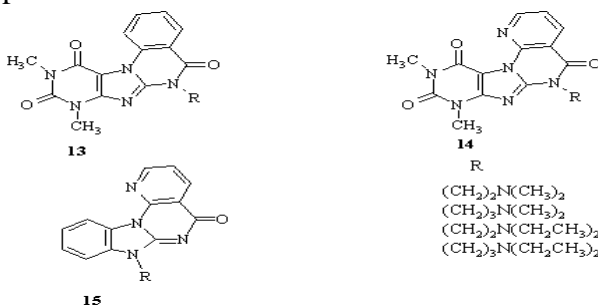
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The chemical modification of methylxanthines especially theophylline derivatives by cyclocondensation of 7,8-disubstituted derivatives yielded tri- or tetra-cyclic system derivatives. The reaction of 8-bromotheophylline with methylhydrazine followed by condensation with acetyl acetate yielded derivative 11 which after intermolecular cyclization gave appropriate triazepino [4,3-t] theophylline 12 [25].

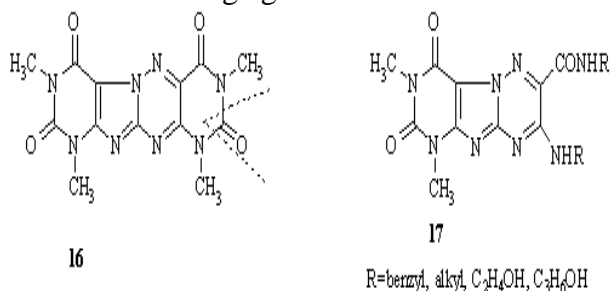


The angular derivatives containing theophylline nucleus as a part of their tetracyclic system of 8,10-dimethylpurino [7,8-a] quinazolino-5,9,11 (6H,8H, 10H) triones 13, 8,10-dimethylpyrido[2',3':4,5]pyrimido[1,2-f]purine-5,9,11 (6H, 8H, 10H)-triones 14 and 5,7-dihydro-5-oxopyrido [3',2':5,6] pyrimido [1,2-a]benzimidazoles 15. Some of the derivatives of 14 and 15 with an alkylamino substituent improve DNA binding properties and were evaluated as anti-proliferative agents [26].

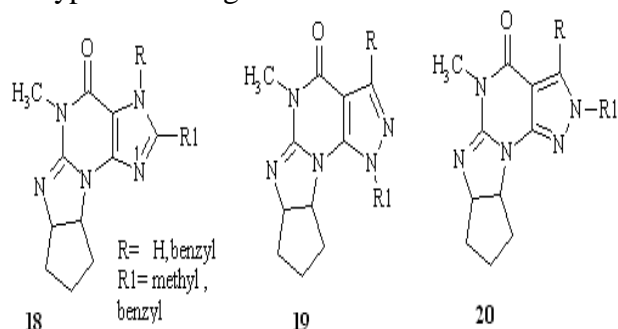
The biological activity of the compounds 13-15 is related to their ability to form a complex with DNA, leading to inhibition of replicative enzymes and DNA repair system interfering with topoisomerases [18].



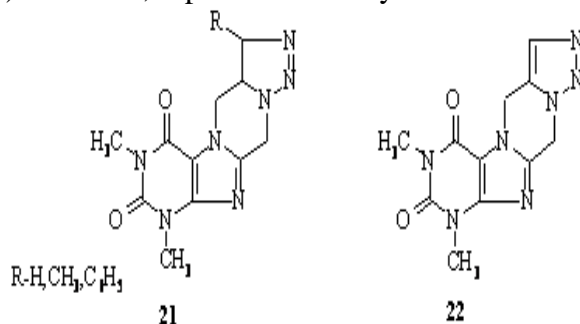
Tetracyclic purine[7,8-g] 6-azapteridines 16 were active against P-388 leukemia. The fourth ring aminolysis of 6-azapteridines with alkylamine gave [1,2,4] triazino [3,2-f] purines 17 examined as vascular relaxing agents [27].



Tetracyclic derivatives chemically related to theophylline were synthesized as guanine phosphodiesterase inhibitors. The structure-activity relationships showed that tetracyclic derivatives (18-20) gave the best combination of potency and selectivity for phosphodiesterases of c- AMP (PDE1, PDE 5) and c-GMP. The compounds were also orally active as antihypertensive agents [27].



Some tetracyclic theophylline derivatives with complex triazolino [1,5-a] pyrazine (21 and 22) fused in 8,9- position were synthesized [27].



They have been showed the activity on the cardiovascular system; particularly they exhibit anti-anginous, anti-arrhythmic activities also antihypertensive effects [29].

#### Therapeutic applications:

During the last few years, the discovery of potent and selective adenosine antagonists luidated physiological roles of adenosine, the receptor in different parts of the body and ,consequently, the possible therapeutic use. Tricyclic and tetracyclic theophylline derivatives useful in the treatment of hypertension through their action at different levels, anti-anginous, anti-arrhythmic activities [29].

Tricyclic and tetracyclic theophylline derivatives with an alkylamino substituent improve DNA binding properties and were evaluated as anti-proliferative agents [26]. Some of them has vascular relaxing property. In contrast to the mother compound (theophylline), all investigated tricyclic derivatives generally exhibited sedative profile of pharmacological activity on CNS, particularly those which contain longer alkyl carboxylic acidrest in 9-position [7].

**CONCLUSION**

From the previous paragraph, it is evident that in contrast to mother theophylline, all investigated tricyclic compounds generally exhibited a strong sedative action, particularly those which contained the basic aminoalkyl side chain, substituted on the third bound ring at N8 of imidazole, N9 of pyrimidine and N10 of diazepam. Their sedative properties were confirmed in a number of behavioral tests [7]. The new compounds are of interest due to their potential pharmacological activities, and they will be useful as standard compounds for treatment of central nervous system as (hypnotic, sedative, hypothermizing properties, anti-epileptic effects and analeptics – like properties), and cardio-vascular system disorders as (anti-hypertensive, anti-arrhythmia activities).

A lot of attempts to synthesis, investigation and evaluated for pharmacological properties (mainly on CNS activity) of tricyclic derivatives in which compared to the mother structure of 1,3-dimethyl xanthines (theophylline). Derivatives of pyrimido or diazepamino [2,1-f]-purinedione or trione containing pharmacophore moieties gave the characteristic of tricyclic neuroleptic or anti-depressants; they have been showed CNS activity different from the activity representative for the parent compound (methyl-xanthines).

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