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Original Research Manuscript

CNS STIMULATION EFFECT OF SEMISYNTHETIC ADDUCT OF CAFFEINE WITH SCHIFF'S BASE OF PYRAZOLONE AND PYRAZOLO-PYRIMIDINE NUCLEUS

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Abstract: The CNS stimulation study has been performed on the two semisynthetic adducts of caffeine with Schiff's base of pyrazolone and pyrazolone-pyrimidine nucleus. All the reference drugs and test compounds showed positive effect on CNS stimulation. The conclusion has been drawn from the fact that CNS stimulation effect for pentylene tetrazole is higher than caffeine, compound-I (pyrazolone ring) is less active than compound-II as the compound-II (pyrazolo-pyrimidine ring) is fused ring heterocyclic compound and the synergistic action with caffeine with compound-I having less activity than the compound-II but in case of leptazol (pentylene tetrazole), the synergistic activity of the two test compounds are equal but less than leptazol itself. The azole group is present in both caffeine and in leptazol but in fused ring heterocyclic chromophore and the same ring has been implemented in the two test compounds which have been semisynthesized by formation of Schiff's base of caffeine to keep the similar bioisosteric nature. So, the components that have been semisynthesized showed the specific CNS stimulation activity.

Keywords: Pyrazolone, pyrazolone-pyrimidine, caffeine, leptazol, CNS stimulation

OBJECTIVES:

Isolation of pure caffeine from tea leaves.

Synthesis of pyrazolo and pyrazolo-pyrimidine nucleus.

Synthesis of semi-synthetic adduct by reacting caffeine with pyrazolo and pyrazolo-pyrimidine nucleus with hydrazine.

Identification of structural framework.

Determination of LD50 values of the semi-synthetic adducts.

Biological screening of the synthesized molecules for CNS stimulation effect with comparison to leptazol.

Design of Work:

Isolation of pure CAFFEINE from tealeaves:

Caffeine is isolated from fresh tealeaves by boiling the leaves with water and the extract is treated with saturated lead acetate solution to remove the plant pigments. The filtrate is then treated with H2S gas to remove the trace of lead ions. The next filtrate is then concentrated and treated with sodium chloride to make it saturated. Then the solution is extracted three times with chloroform to separate caffeine as in organic phase. The organic phase is then treated with anhydrous sodium sulphate to make it moisture free. Crude caffeine was obtained by evaporation of chloroform layer. Crystallization has been done from aqueous alcohol [1].

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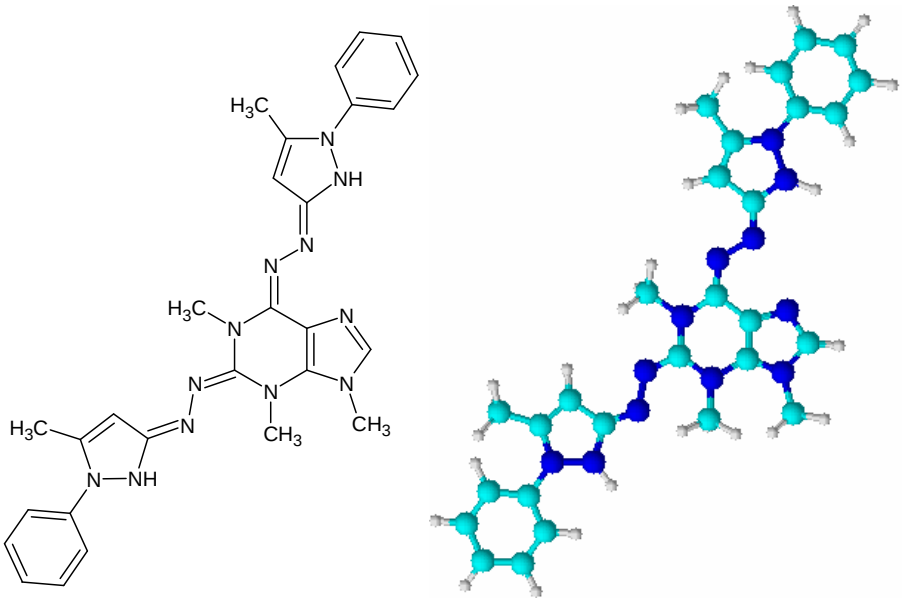
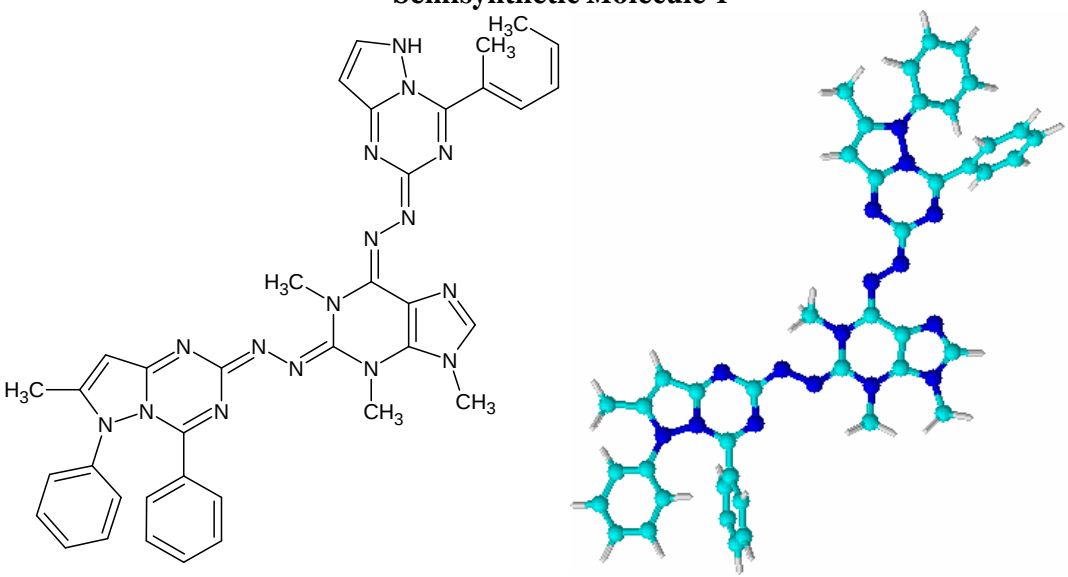


Semisynthetic Molecule-I

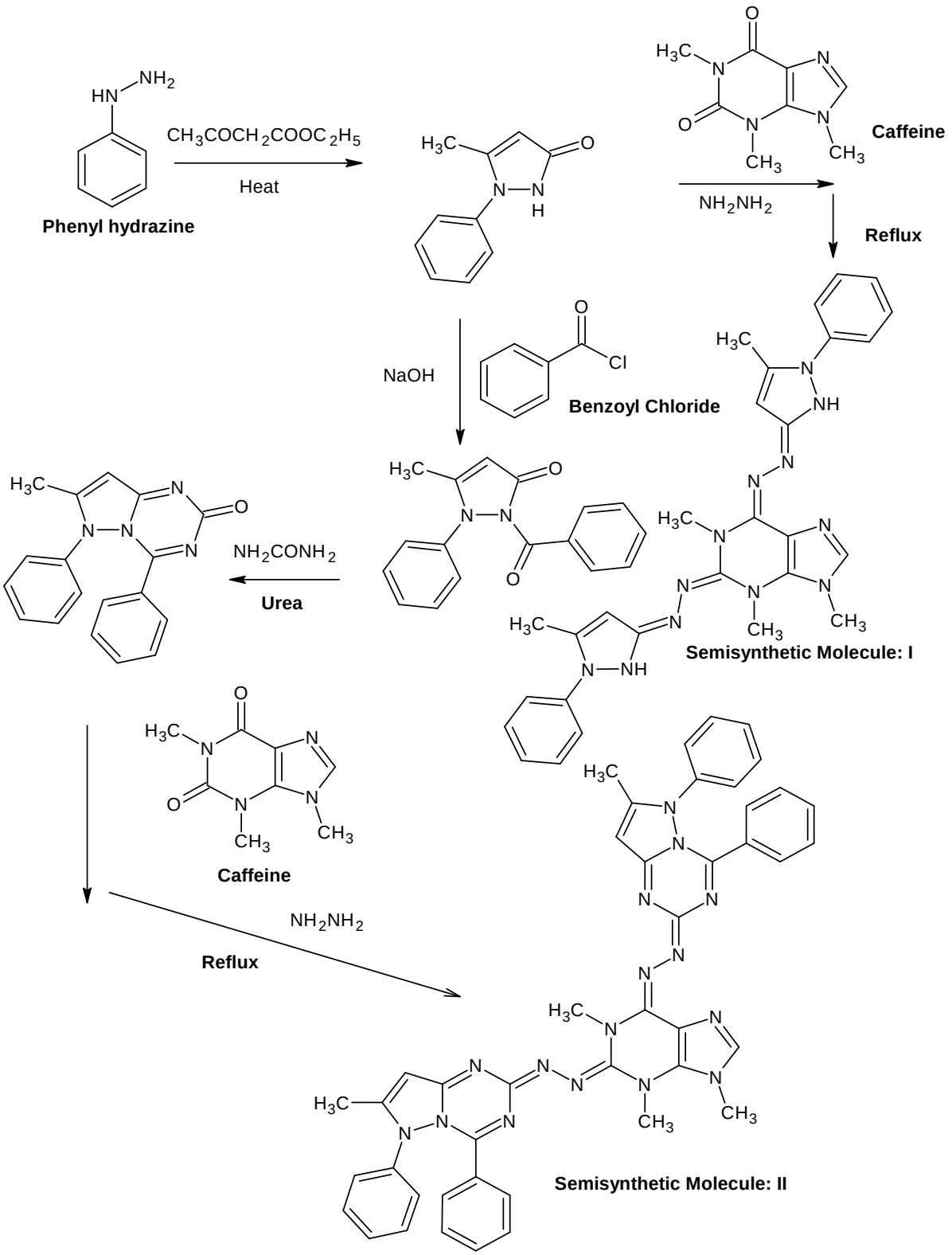


Semisynthetic Molecule-II

SYNTHESIS OF SEMISYNTHETIC ADDUCTS:

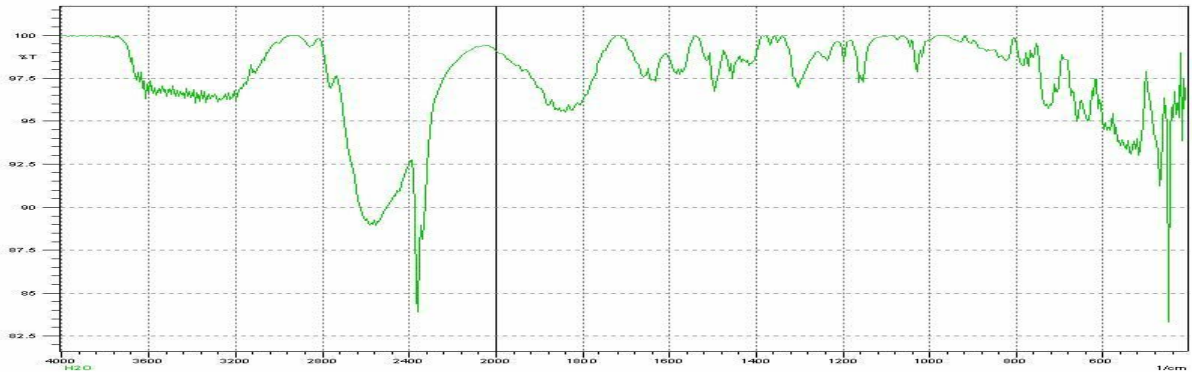
Phenyl hydrazine is condensed with ethyl acetoacetate to get the 5-pyrazolone heterocyclic rings, which on reacting with caffeine and hydrazine produces SEMISYNTHETIC MOLECULE-I and 5-pyrazolone heterocyclic rings reacting with urea produces pyrazolo-pyrimidine nucleus, which on reaction with caffeine with hydrazine produces SEMISYNTHETIC MOLECULE-II. These are then characterized by melting points, IR Spectra and N% [2,3].

SCHEME

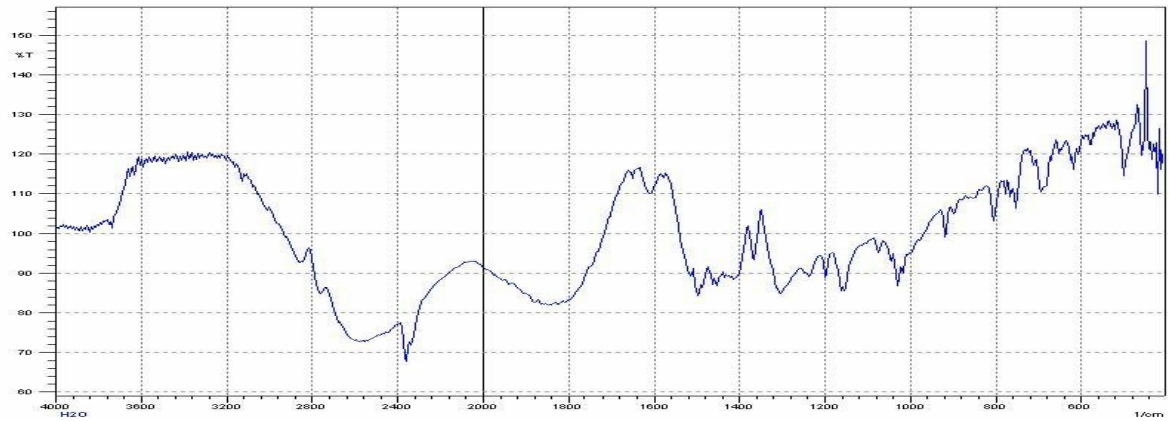


INFRARED spectroscopy

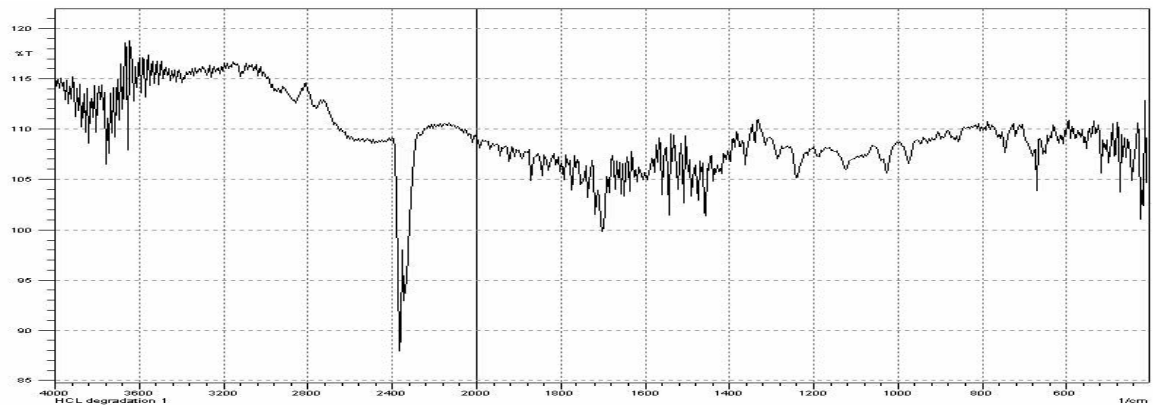
CAFFEINE



CAFFEINE WITH PYRAZOLO-PYRIMIDINE ADDUCT: SEMISYNTHETIC MOLECULE-I

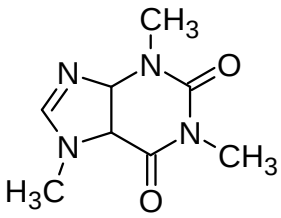


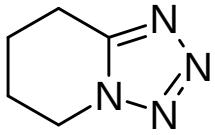
CAFFEINE WITH PYRAZOLO-PYRIMIDINE ADDUCT: SEMISYNTHETIC MOLECULE-II



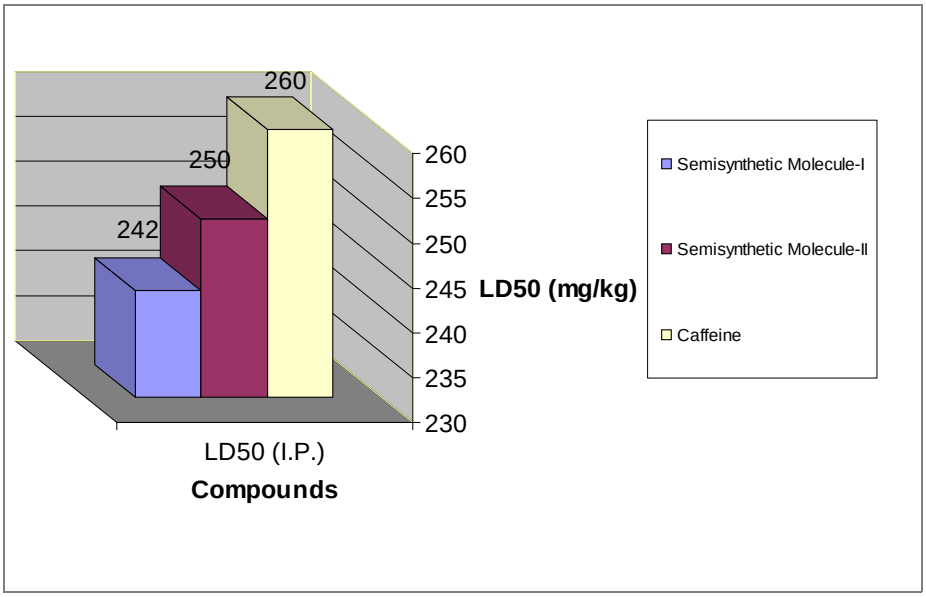
Physicochemical PARAMETERS:

Items	Melting Point ºC	N% Calculated	N%Found	Molecular Formula
Semisynthetic Molecule-I (44%)	238	30.21	31.03	$C_{28}H_{30}N_{12}$
Semisynthetic Molecule-II (52%)	292	18.12	17.94	$C_{44}H_{40}N_{16}$
	Caffeine		Pentylene tetrazole (Leptazol)	





ACUTE TOXICITY STUDIES



Compounds	CNS Stimulation	Potency
Caffeine	+	
Leptazol	++	1.Caffeine Group Ξ Caffeine + Compound-I Group) <
Semisynthetic Molecule-I	+	(Caffeine + Compound-II)
Semisynthetic Molecule-II	++	2. Leptazol Group > (Leptazol + Compound–I) Ξ
Caffeine+ Semisynthetic Molecule-I	+	(Leptazol + Compound-II)
Caffeine+ Semisynthetic Molecule-II	++	3. Compound-I < Compound –II
Leptazol+ Semisynthetic Molecule-I	++	4. Caffeine Group < Leptazol Group
Leptazol+Semisynthetic Molecule-II	++	

PHARMACOLOGICAL SCREENING

CONCLUSION:

Caffeine Group Ξ (Caffeine + Compound-I Group) < (Caffeine + Compound-II)

Leptazol Group > (Leptazol + Compound–I) Ξ (Leptazol + Compound-II)

Compound-I < Compound –II

Caffeine Group < Leptazol Group

All the reference drugs and test compounds showed positive effect on CNS stimulation. The conclusion has been drawn from the fact that CNS stimulation effect for pentylene tetrazole is higher than caffeine, compound-I (pyrazolone ring) is less active than compound-II as the compound-II (pyrazolo-pyrimidine ring) is fused ring heterocyclic compound and the synergistic action with caffeine with compound-I having less activity than the compound-II but in case of leptazol (pentylene tetrazole), the synergistic activity of the two test compounds are equal but less than leptazol itself [4]. The azole group is present in both caffeine and in leptazol but in fused ring heterocyclic chromophore and the same ring has been implemented in the two test compounds which have been

semisynthesized by formation of Schiff's base of caffeine to keep the similar bioisosteric nature. So, the components that have been semisynthesized showed the specific CNS stimulation activity [5].

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References:

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