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SYNTHESIS OF NOVEL PYRAZOLO [3,4-d] PYRIMIDIN[3,4-a] THIAZOLIDINONES

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ABSTRACT :

Heterocyclic bearing nitrogen and sulphur atoms constitute the core structure of a number of biologically interesting compounds. Pyrazole derivatives are well established in the literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due to their wide spread potential biological activities such as antifungal [1], anti diabetic [2], herbicidal [3], antifertility[4], sedative [5] and antimicrobial activities [6], etc. Phthalimidoxy and other aminoxy compounds are known to possess wide range of biological activities like antimalarial,CNS depresant, antihypeertensive and antimicrobial activities [7-1O].

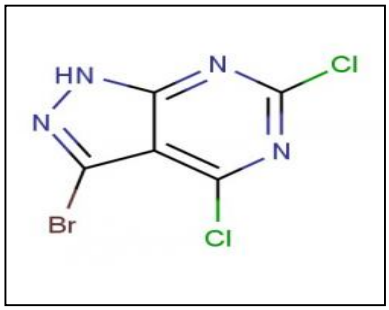
KEYWORDS : *Heterocyclic bearing nitrogen , Pyrazole derivatives , anti diabetic.*

INTRODUCTION

Some of pyrazole derivatives which have been prepared as neuroleptics and a propanone derivative showed moderate *in vitro* cyclotoxic activity. A potent kinase inhibitor pyrazole derivative 1,3-di-ter-butyl-N-(4-flurophenyl)-1 ,6-dihydroimidazo[4,5-c]pyrazole-5- amine has been found in Nested chemical library (NCC TM) during a high through put screening (HTS) kinase assay.

Pyrimidine and its derivatives are important structural motifs in medicinal and pharmaceutical chemistry. They are known to exhibit promising physiological [11] and biological properties such as antimicrobial [12] and anticonvulsant behavior [13]. They are also known to possess antibacterial and antifungal activities. Recently, Marugan et al. [14] have reported the biological activity of these molecules as antagonists for neuropeptide S receptor (NPSR) [15]. The NPSR represents a novel drug targets for the treatment of sleep, anxiety, and addiction disorders [16].

Thiazolidinones and thiazolidinediones were the first parent compounds m which thiazole ring was recognized [17]. A large number of thiazolidinones are reported in literature for their biological activities such as anticonvulsant [18] anti-inflammatory [19,20], hypnotic[21], amoebicidal [22], analgesic[23], anti AIDS [24], etc. 4-Thiazolidinone derivatives substituted at 2, 3, 4 or 5 positions are antidiabetic drugs [25].



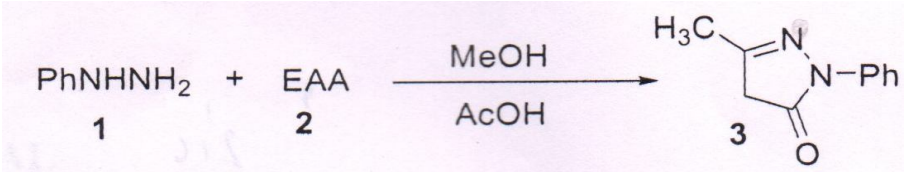
Prompted by the impressive biological properties of pyrazoles, pyri midines and thiazolidinones into consideration in our present investigation, we synthesized a series of pyrazolopyrimidi nthiazolidi nones.

RESULTS AND DISCUSSION

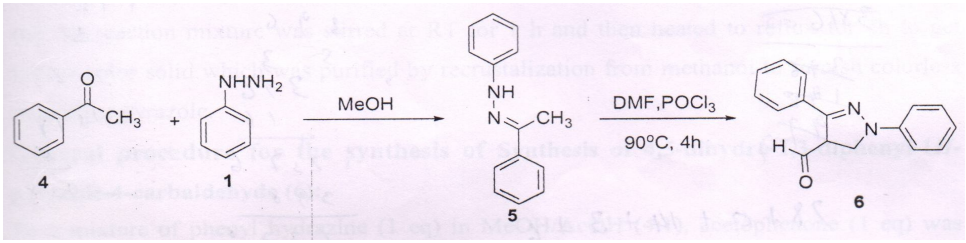
The startening materias used in the present i.e. pyrazoles were prepared by the reaction of phenyl hydrazine with ethyl acetoacetate **(Scheme 1a).** The pyrazole aldehyde as prepared by strating from the condensation acetophenone and phenyl hydrazine followed Vilsmeier-

Haack formylation of corresponding phenyl hydrazone **(Scheme 1b).**

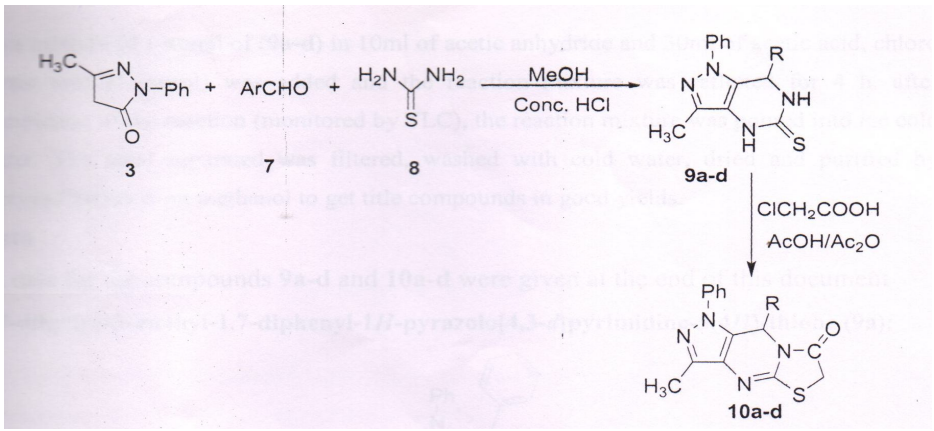
The pyrazolopyrimidines were prepared by one-pot three component reaction of pyrazole, aldehydes and thiourea which is generally known as Biginelli dihydropyrimidine reaction. These pyrimidines later on cyclization with chloacetic acid gave title compounds **(Scheme 2)** in good yields. All the synthesized compounds were confirmed by TLC, m.p, and IR data. The data were given in experimental section.



Scheme 1a: synthesis of 3-methyl-1-phenyl-1H-pyrozole-5(4H)-one



Scheme 1b: Synthesis of 4,5-dihydroxy-1,3-diphenyl-1H-pyrazole-4-carbaldehyde



Scheme 2 : Synthesis of pyrazolo[3,4-d]pyridine[3,4]thiazolidones

OBJECTIVES

1) To synthesis different novel thiazolidinones and derivatives with several structural variations and their purification using crystallization and chromatographic techniques.
2) To charecterize synthesised heterocycles using spetroscopic techniques and elemental analysis.
3) To evaluate the Biological activity of synthesised compounds against some selected pathogens and comparision with molecules of biological importance

work plan

Total duration 3 years

First year

To synthesise different novel thiolidinones and its derivatives with several structural variations and their purification using crystallization techniques.

Second year

To Charecterise synthesised heterocycles using spectroscopic techniques and elemental analysis.

Third year

To evaluate the Biological activity of synthesised compounds against some selected pathogens and comparision with molecules of biological importance

General procedure for the synthesis of 3 methyl-1-phenyl-1H-Pyrazol-5(4H)-one(3):

To a mixture of phenyl hydrazine (1 mL) in methanol/AcOH (4:1) , EAA (1.5 mL) was added and the reaction mixture was stirred at Rt for 1 hour and then heated to reflux for 4 hours to get yellow color solid which was purified by recrystalization process from methanol to furnish colorless crystalline pyrazole.

General procedure for the synthesis of 4,5-dihydro-1,3-diphenyl-1H-pyrazole-4-carbaldehyde (6):

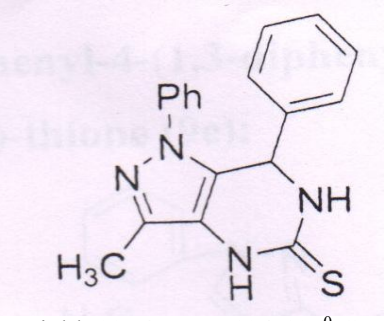
To a mixture of phenyl hydrazine (1 eq) in MeOH AcOH (4:1), acetophenone (1 eq) was added and the reaction mixture was stirred at RT for 1 hour to get yellow color phenyl hydrazone. To the cooled solution of DMF (0.0014) , $PoCl_3$ (0.0014 mol) was added drop wise 30 minutes by maintaining the temperature of 0-5 ^{0} C . To this solution phenyl hydrazene 1 eq) was added and stirred the reaction mixture for 6 h at room temperature . After completion of reaction (monitored by TLC), the reaction mixture was poured into ice - cold water , the solid separated was filtered , washed with cold water and purified by recrystalization process from MeOH.

General procedure for the synthesis of pyrazole [3,4-d]pyridin-5 thiones (9a-d), and of pyrazole [3,4-d]pyridin [3,4-a]thiazolidinones(10a-d):

A mixture of (2 mmol) , aldehyde (2 mmol) and thiourea (2 mmol) in MeOH with catalytic amount of conc.HCl was refluxed for 12 h to get pyrazolopyrimidines (9a-d) , which were purified by recrystallization from MeOH.

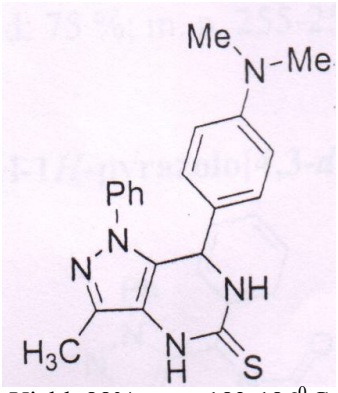
To a mixture of 1mmol of (9a-d) in 10 ml of acetic anhydride and 30ml of acetic acid , chloro acetic acid (1 mmol) was added and the reaction mixture was refluxed for 4 h , after completion of the reaction (monitored by TLC) , the reaction mixture was poured into a ice-cold water ,dried and purified by recrystallization process from methanol to get title compounds in good yields.

6,7-dihydro-3-methyl-1,7-diphenyl-1H-pyrazolo[4,3-d]pyrimidine-5($H)-thione (9a):



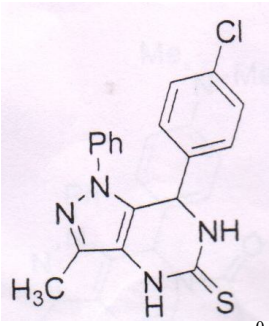
yield: 83 % ; m.p .124-126^0 C

7-(4-)dimethyllamino)-phenyl)-06,7-dihydro-3-methyl-1-phenyl-1H-pyrazolo[4,3-d] pyimedine-5(4H)-thione(9b):



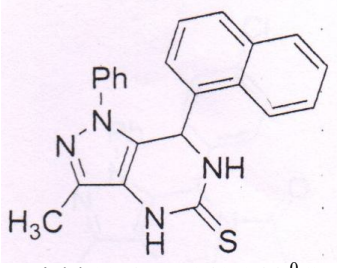
Yield: 88%; m.p. 183-186^{0}C

7-(4-chlorophenyl)-6,7-dihydro-3-methyl-1-phenyl-1H-pyrazolo[4,3-d]pyrimidine-5(4H)-thione(9c):



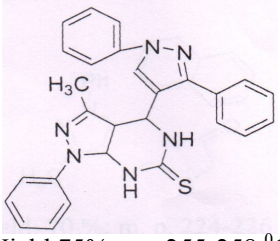
Yield:81%;m.p.254-256^{0}C

6,7-dihydro-3-methyl-7-(naphthalen-1-yl)-1-phenyl-1H-pyrazolo[4,3-d]pyrimidine-5(4H)-thione(9d):



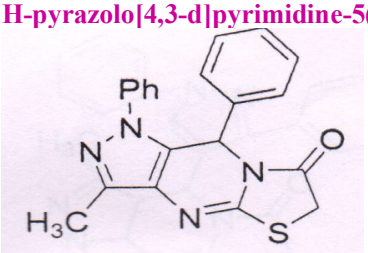
Yield:82%m.p.242-244 ^{0}C

4,5,7,7a-tetrahydro-3-methyl-1-phenyl-4-(1,3-diphenyl-H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidine-6(3aH)-thione(9e):



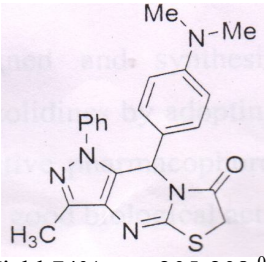
Yield:75%;m.p.255-258 ^{0}C

6,7-dihydro-3-methyl-1,7-diphenyl-1H-pyrazolo[4,3-d]pyrimidine-5(4H)-thione(10a):



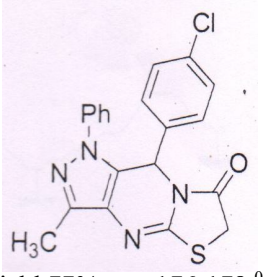
Yield:78m.p.212-214 ^{0}C

7-(4-(dimethylamino)phenyl)-6,7-dihydro-3-methyl-1-phenyl-1H-pyrazolo[4,3-d]pyrimidine-5(4H)-thione(10b):



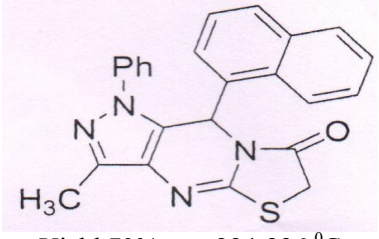
Yield:74%;m.p.205-208 ^{0}C

7-(4-chlorophenyl)-6,7-dihydro-3-methyl-1-phenyl-1H-pyrazolo[4,3-d]pyrimidine-5(4H)-thione(10c):



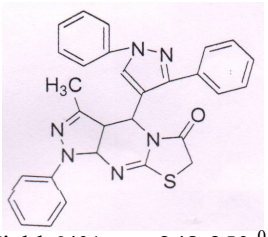
Yield:77%:m.p.176-178 ^{0}C

6,7-dihydro-3-methyl-7-(naphthalen-1-yl)-1-phenyl-1H-pyrazolo[4,3-d]pyrimidine-5(4H)-thione(10d):



Yield:70%;m.p.224-226 ^{0}C

4,5,7,7a-tetrahydro-3-methyl-1-phenyl-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1H-pyrazolo[3,4-d]pyrimidine-6(3aH)-thione(10e):



Yield:64%;m.p.248-250 ^{0}C

CONCLUSION

In conclusion we have designed and synthesized a series of some novel pyrazolopyrimidines and its thiazolidines by adopting simple and elegantprocedures . These compounds are having active paramacophores like pyrozole, pymidine and thiazolidinones , which may show good biological activity.

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