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REVIEW ON SYNTHESIS AND APPLICATIONS OF PYRAZOLOPYRIMIDOPYRIMIDINE SCAFFOLD

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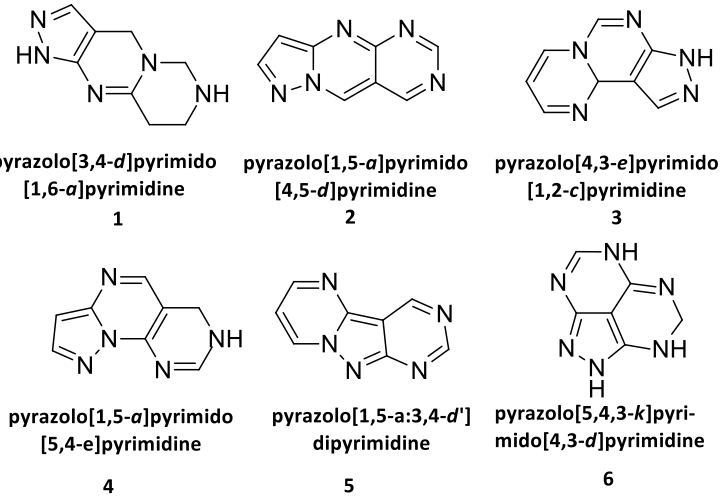
ABSTRACT

Synthesis of variety of pyrazolopyrimidopyrimidines of the type linear and angular such as pyrazolo[3,4-*d*]pyrimido[1,6-a]pyrimidine **1**, pyrazolo[1,5-*a*]pyrimido[4,5-d]pyrimidine **2**, pyrazolo[4,3-*e*]pyrimido[1,2-*c*]pyrimidine **3**, pyrazolo[1,5-*a*]pyrimido[5,4-*e*]pyrimidine **4**, pyrazolo[1,5-*a*]pyrimido[3,4-*d'*]pyrimidine **5** and pyrazolo[4,5,3-*k*]pyrimido[3,4-*d*]pyrimidine **6** have been reported since 1956 in order to discuss some of the structural pathways and with their synthetic and biological importance.



KEWORDS

Pyrazolopyrimidopyrimidines, pyrazolopyrimidines, Pyrazolo[3,4-d]pyrimido[1,6-a]pyrimidine; Pyrazolo[1,5-a]pyrimido[4,5-d]pyrimidine, Pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine, Pyrazolo[1,5-a]pyrimido[5,4-e]pyrimidine; Pyrazolo[1,5-a]pyrimido[3,4-d']pyrimidine, Pyrazolo[4,5,3-k]pyrimido[3,4-d]pyrimidine

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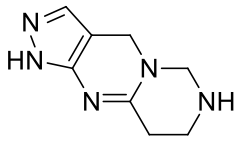
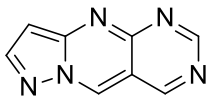
INTRODUCTION

The present review relates pyrazolopyrimidopyrimidines and importance thereof since 1956. Pyrazolopyrimidines have received special attention because of the structural relevance to biogenic purine class compounds, having high impact in the field of pharmaceutical and biotechnological sciences with vast spectrum of biological activities[i-ix] Drugs like Lorediplon, Zaleplon, Divaplon, Ocinaplon, Indiplon, Acetildenafil, PP2, BAY 73-6691, Allopurinol and Oxypurinol based on pyrazolopyrimidine have been reported as anti-insomnia agents, inhibitor for GABAA receptor in the brain, anxiolytic agents, phosphodiesterase inhibitor, kinase inhibitor, effective anti-alzheimer agents, high blood uric acid regulators and also as xanthine oxidase.[v-xv] Pyrimidopyrimidines also displayed significant impact in the field of medicinal chemistry.[xv-xvi] Medicinal chemists are always in search of lead compound. Combining two active moieties, synthesis of linear and angular pyrazolopyrimidopyrimidines with varied fusion **1-6** have been reported since 1956 in order to demonstrate their structural pathways, synthetic importance as well as biological activities.



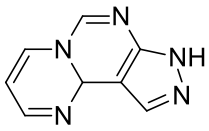
pyrazolo[3,4-*d*]pyrimido [1,6-*a*]pyrimidine

1



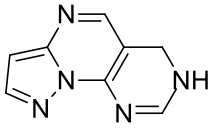
pyrazolo[1,5-*a*]pyrimido [4,5-*d*]pyrimidine

2



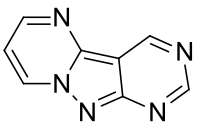
pyrazolo[4,3-*e*]pyrimido [1,2-*c*]pyrimidine

3



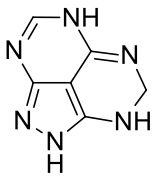
pyrazolo[1,5-*a*]pyrimido [5,4-e]pyrimidine

4



pyrazolo[1,5-a:3,4-*d*'] dipyrimidine

5



pyrazolo[5,4,3-*k*]pyri-mido[4,3-*d*]pyrimidine

6

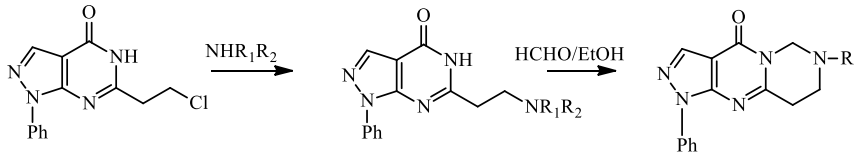
The study revealed synthesis of various linear and angular pyrazoloprimidopyrimidines along with their synthetic and biological importance. Pyrazoloprimidopyrimidines been classified depending on difference in fusion.

1.1 Linear pyrazolopyrimidopyrimisines and their biological activities **(1-2)**

1.1.1 Pyrazolo[3,4-d]pyrimido[1,6-a]pyrimidine

A. M. Elkhawaga *et al*[xvii] synthesized linear pyrazolopyrimidopyrimidines like 1-phenyl-7-aryl-4,5,6,7,8,9-hexahydropyrazolo[3,4-*d*]pyrimido[1,6-*a*]pyrimidine-4-ones **(9)** starting from 6-(2-chloroethyl)pyrazolopyrimidin-2-one **(7)** by reacting it with substituted hydrazines followed by addition of carbon donor moiety in presence of ethanol (scheme 5).

Scheme 1



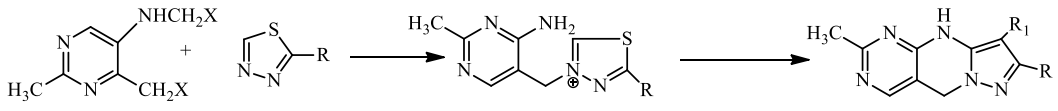
7 **8** **9**

Where R_1= H, R_2 = Ph, R_1= H, R_2 = C_6H_4Cl-p R_1= H, R_2 = C_6H_4Me-p, R_1= H, R_2 = C_6H_4-OMe-p , R_1, R_2 = -$(CH_2)_5$ R_1, R_2 = -$(CH_2)_4O$

1.1.2 Pyrazolo[1,5-a]pyrimido[4,5-d]pyrimidine

Synthesis of linear pyrazolopyrimidopyrimidines[xviii] has been carried out with the aim to investigate them as analgesic, antipyretic and or anti-inflammatory agents, in addition synthesis aimed to provide useful intermediate to synthesize such active agents. Synthesis of pyrazolopyrimidopyrimidines of the type **12** was reported by following four different routes[xix-xx] (scheme 1-4). In the first route 4-amino-5-halogenomethyl-2-methylpyrimidines **(9)** were treated with 1,3,4-thiadiazole compounds **(7)** to yield the corresponding 1,3,4-thiadiazolium salts, and then reacting the latter with diethyl benzoyl phosphonate to give **12**. The reaction sequence is presented in scheme 2.

Scheme 2

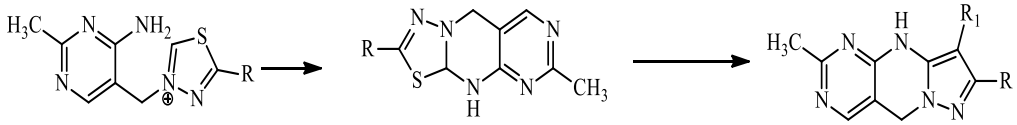


10 **11** **12**

where X=halide, R=lower alkyl, phenyl, (phenyl)lower alkyl, halide, R1=H, Cl

Second route involved the reaction of thiadiazolopyrimidopyrimidines **(11)** with phosphorus compounds such as di(lower) alkyl benzoyl phosphonates (e.g. diethyl benzoyl phosphonate, dimethyl benzoyl phosphonate) and lower alkyl phenyl benzoyl phosphinates (e.g. methyl phenyl benzoyl phosphinate, ethyl phenyl benzoyl phosphinate) giving the formation of required pyrazolopyrimidopyrimidines **(12)** through the formation of compounds **13** (scheme 3).

Scheme 3

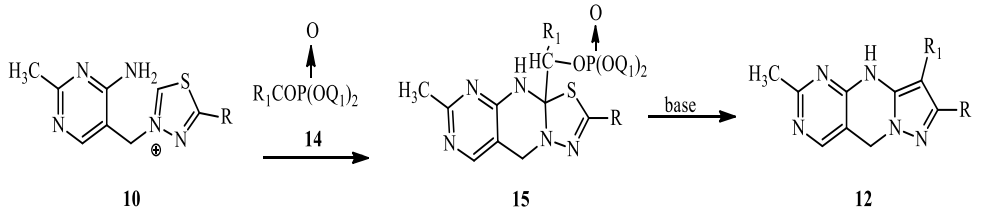


11 **13** **12**

where R=lower alkyl, phenyl, (phenyl)lower alkyl, halide, R1=H, Cl

Route 3 described the reaction between 3-[(4-amino-2-methylpyrimidin-5-yl)methyl)]-5-methyl-1,3,4-thiadiazol-3-ium salts **(10)** with phosphoryl compounds **(14)** forming the intermediate compounds **(15)** which on treatment with base afforded the same pyrazolopyrimidopyrimidines **(11)** (scheme 4).

Scheme 4

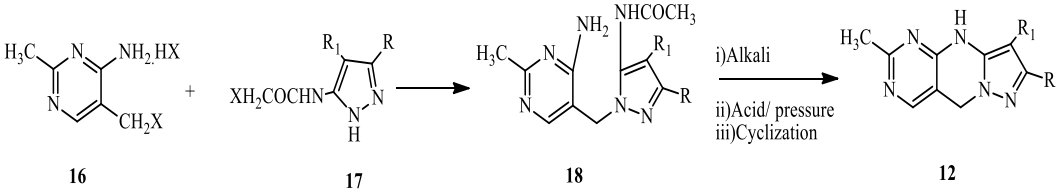


10 15 12

where R=lower alkyl, phenyl, (phenyl)lower alkyl, halide, R1=H, Cl, Q1=lower alkyl

The fourth route included the reaction of 4-amino-5-halogenomethyl-2-methylpyrimidines **(16)** with *5H*-acetamidopyrazoles **(17)**, hydrolyzing the resulting products with an alkali and treating the resulting 2-methyl-4-amino-5-(5-aminopyrazol-l-ylmethyl)pyrimidines **(18)** with an acid to give hydroxyl derivative which followed cyclization to form intended pyrazolopyrimidopyrimidines **(12)** (scheme 5).

Scheme 5

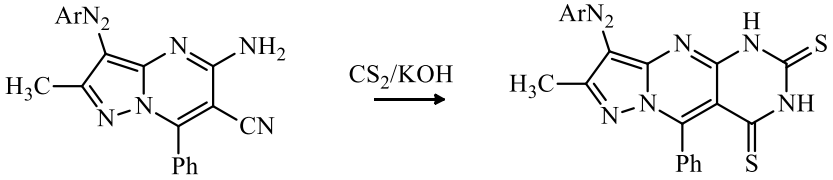


16 17 18 12

where R=lower alkyl, phenyl, (phenyl)lower alkyl,,halide, R1=H, Cl

Synthesis of 3-(4-chlorophenylazo)-2-methyl-9-phenylpyrazolo[1,5-*a*]pyrimido[4,5 *d*]pyrimidin-6,8-dithione **(21)** was reported from 5-Amino-3-(4-chlorophenylazo)-2-methyl-7-phenylpyrazolo[1,5-a]pyrimidine-6-carbonitrile **(20)** on treatment with carbon disulphide in presence of KOH. The compound was tested for antibacterial and antifungal activity[xxi] (Scheme 6).

Scheme 6

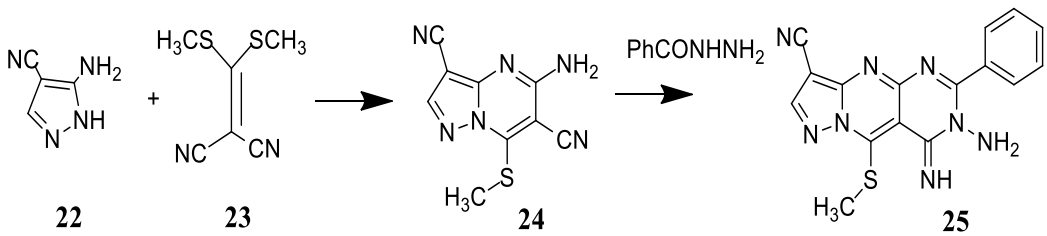


20 21

Where Ar= 4-ClPh

5-Amino-7-(methylthio)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile (**24**) prepared from pyrazole (**22**) and 2-(bis(methylthio)methylene) malononitrile (**23**), on treatment with PhCONHNH2 to give 3-amino-4-imino-5-(methylthio)-2-phenyl-3,4-dihydropyrazolo[1,5-a]pyrimido [4,5-d]pyrimidine-9-carbonitrile[xxii] (**25**) (Scheme 7).

Scheme 7



22 23 24 25

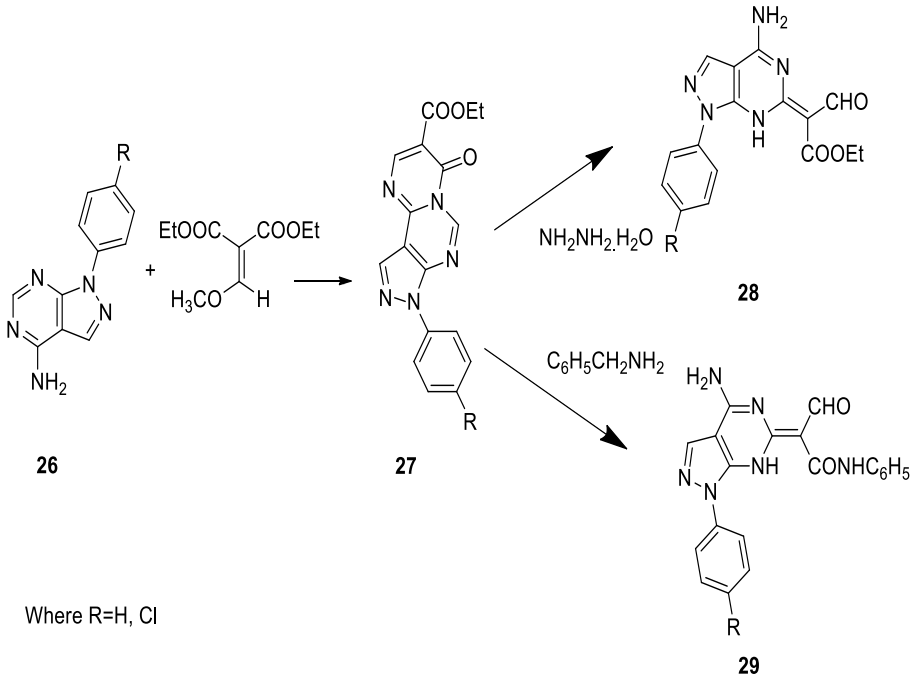
1.2 Angular pyrazolopyrimidopyrimidines and their biological activities **(3-6)**

1.2.1 Pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine

Heba A. Abd El Razik, and Abeer E. Abdel Wahab[xxiii] synthesized angular pyrazolopyrimidopyrimidines such as ethyl 8-aryl-4-oxopyrazolo[4,3-*e*]pyrimido[1,2-

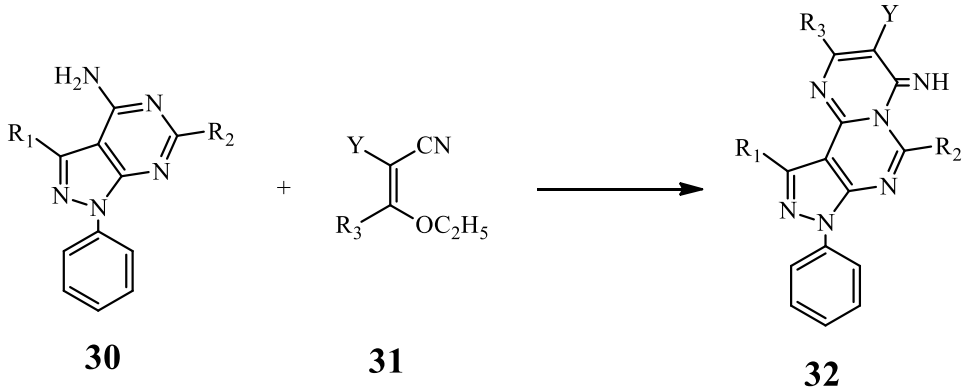
c]pyrimidine-3-carboxylates **(27)** from corresponding pyrazolopyrimidine-4-amines **(26)** and investigated them as anticancer and antimicrobial agents, compound **27** on treatment with hydrazine hydrate and benzyl amine respectively found to undergo ring opening of pyrimidine ring to give respective 4-aminopyrazolopyrimidines **28** and **29** (scheme 8).

Scheme 8



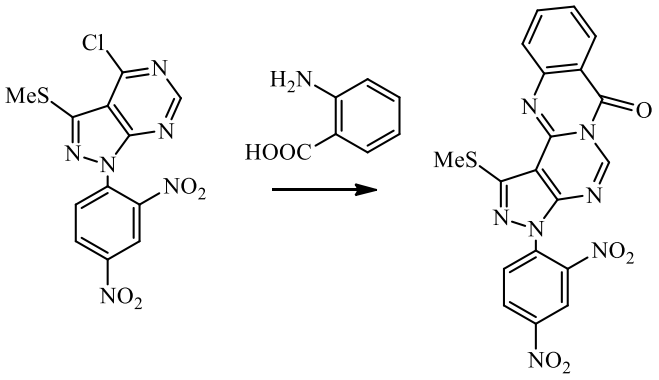
Amine Karoui[xiv] reported angular pyrazolopyrimidopyrimidines such as 1-phenyl-3,9-disubstituted 6-carbethoxy or 6-cyano-7-imino-1,7-dihydropyrazolo[4,3-*e*]pyrimido[1,2-*c*]pyrimidine derivatives **(32)** from condensation of respective 4-aminopyrazolopyrimidines **(30)** and 2-(ethoxymethylene)malononitrile or E)-ethyl 2-cyano-3-ethoxyacrylate derivatives **(31)**. The synthesized compounds were tested for anti-inflammatory activity with gastro protective effect in rats (scheme 9).

Scheme 9



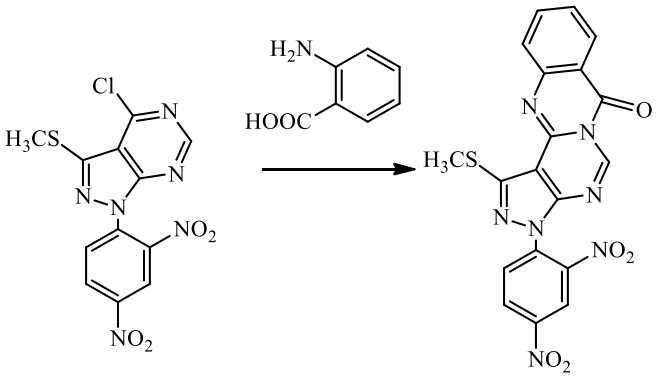
Fathalla *et al*[xxv-xxvi] synthesized benzo fused pyrazolopyrimidopyrimidine derivatives such as 8-[(7-Chloroquinolin)-1-methylsulfanyl-*3H*-2,3,4,5a,11-pentaaza-cyclopena[*a*]anthr-acen-6-one **(34)** and 8-[(2,4-dinitrophenyl)-1-methylsulfanyl-*3H* 2,3,4,5a,11-pentaaza-cyclopena[*a*]anthracen-6-one **(36)**. Compounds **34** & **36** were prepared from reaction between respective 4-chloropyrazolo[3,4-*d*]pyrimidines **(33&35)** and anthranilic acid by classical heating in n-butanol (scheme 10 and 11).

Scheme 10



33 34

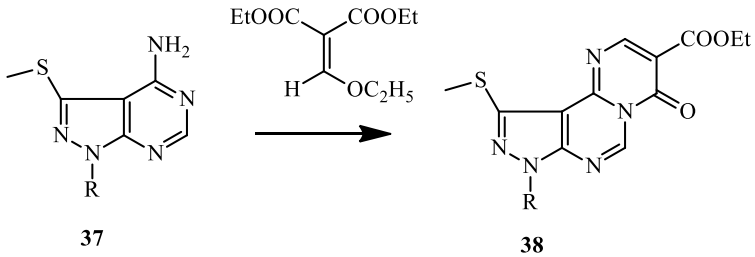
Scheme 11



35 **36**

Shah R D et al[xvii] synthesized ethyl 8-substuted10-(methylthio)-4-oxo-4,8-dihydropyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylates (**37**) from 4-aminopyrazolopyrimidines (**38**) by and EMME with and without microwave heating (scheme 12).

Scheme 12

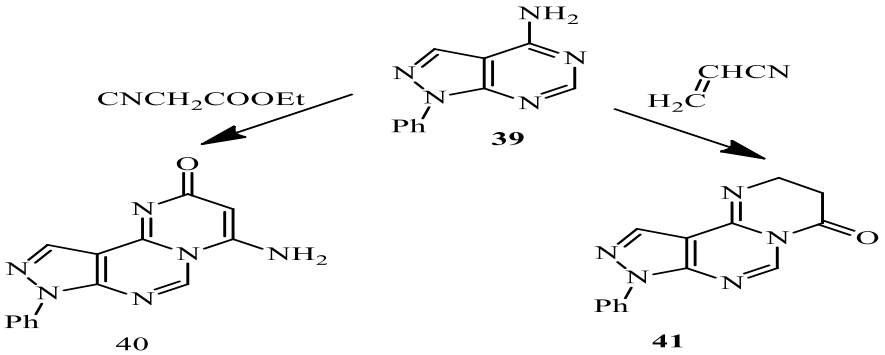


37 **38**

where R= substituted phenyl, heteroaryl

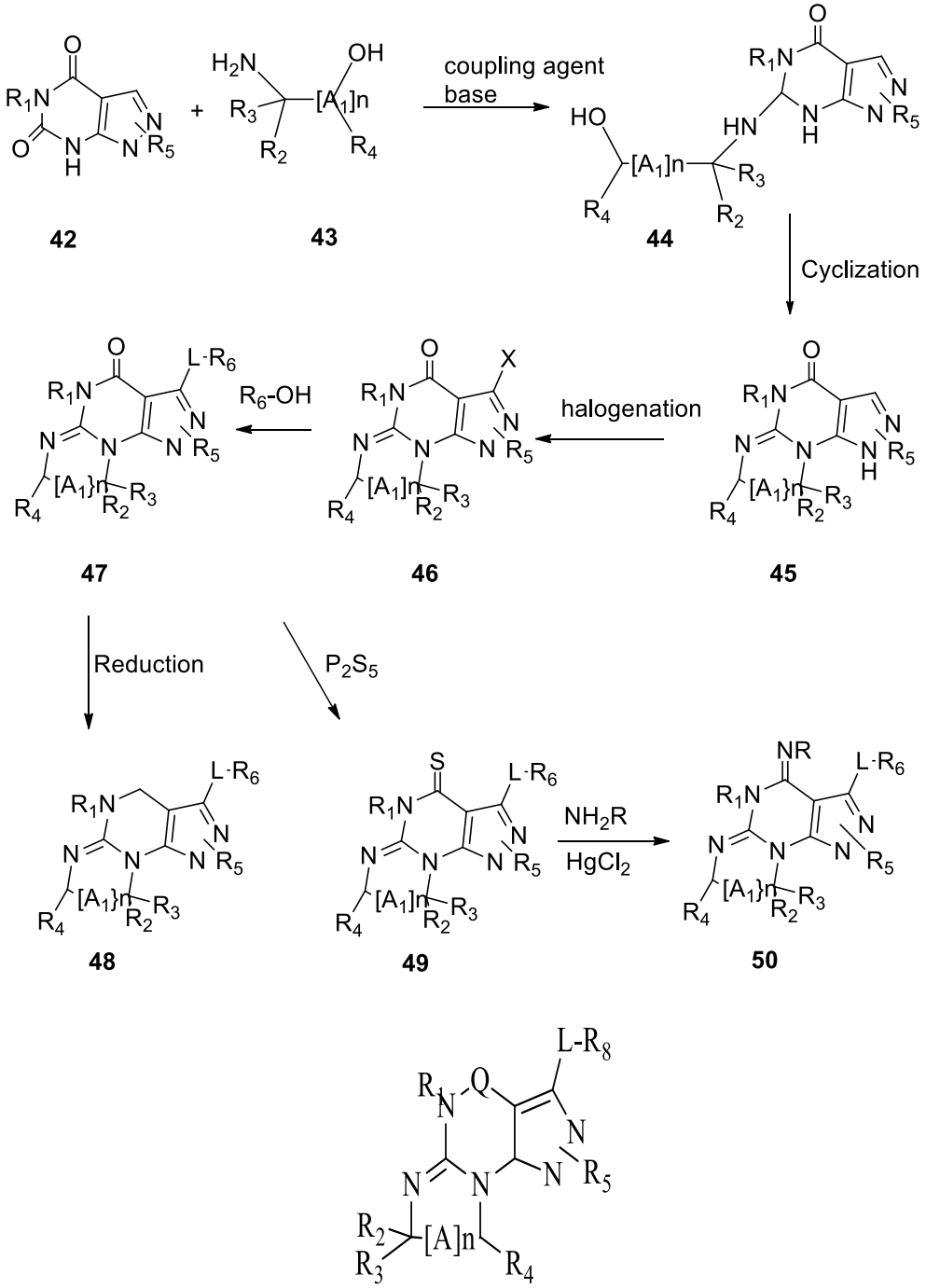
M.Abdel-Megid *et al*[xviii] reported the reaction of 1-phenylpyrazolo[3,4-*d*]pyrimidine-4-amines **(39)** with ethyl cyanoacetate or acrylonitrile forming respective cyclized product such as 4-Amino-8-phenylpyrazolo[4,3-*e*]pyrimido[1,2-*c*]pyrimidine **(40)** and 8-phenyl-2,3-dihydropyrazolo[4,3-*e*]pyrimido[1,2-*c*]pyrimidin-4-one **(41)** (Scheme 13).

Scheme 13



Synthesis of various pyrimido[1,2-*a*]pyrazolo[4,3-e]pyrimidines (**45-50**) was attempted to prepare pharmaceutically accepted acid or base salts of particular interest which were useful inhibitors of phosphodiesterase (PDE1) in the treatment of diseases involving the disorders of Dopamine D1 receptor intracellular pathways in Parkinson's disease, depression, narcolepsy, damage to cognitive function e.g., in schizophrenia, or disorders that may be ameliorated through enhanced progesterone-signaling pathway, e.g., female sexual dysfunction[xxix]. The intended pyrazolopyrimidopyrimidines **45-50** were prepared by following sequential reactions starting from **42** & **43** through the formation of **44** as shown in scheme 14.

Scheme 14



45-50

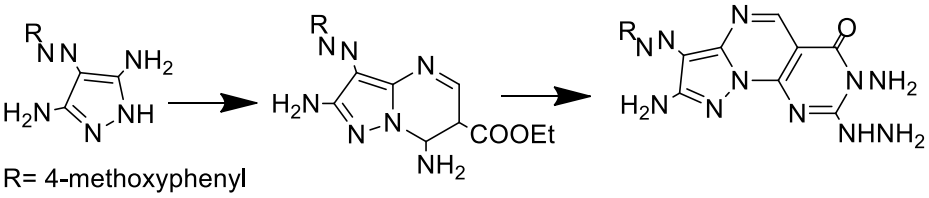
Where Q= CH_2, C=O, C=S,C=NR_{20}, L=O, R_1=R_4= H, C_{1-4} alkyl, R_2=R_3=H, C_{1-4} alkyl, alkoxy, R_6=C_{1-4} alkyl, C_{3-7} cycloalkyl, aryl, substituted heteroaryl, alkylaryl, alkoxy aryl etc., R_{20}=H, C_{1-4} alkyl, C_{1-4} alkyl, C_{3-7} cycloalkyl, A= ($CR_{13}R_{14}$), n=$_1$, R_{13}=R_{14}=H, Cl,C_{1-4} alkyl, aryl, substituted heteroaryl, di-tri and tetraethylene bridged with R_3 or R_4

1.2.2 Pyrazolo[1,5-*a*]pyrimido[5,4-*e*]pyrimidine

Pyrazoles **51** was treated with ethyl-2-cyano-3-ethoxyacrylate to give Ethyl-2,7-diamino-3-([4-methoxyphenyl]diazenyl)pyrazolo[1,5-*a*] pyrimidine-6-carboxylates (**52**) which on

treatment with thiocarbohydrazide gave 3,8-diamino-2-hydrazineyl-7-([4-methoxyphenyl]diazenyl) pyrazolo[1,5-a]pyrimido[5,4-*e*]pyrimidin-4(3H)-ones (**53**)[xxx] (Scheme 15)

Scheme 15

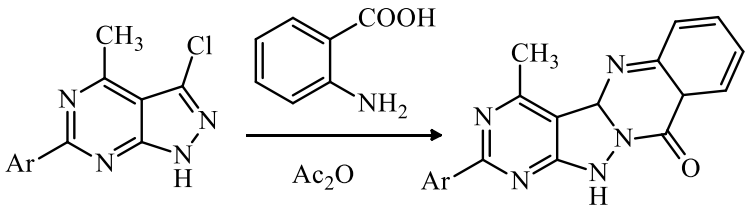


51 **52** **53**

1.2.3 Pyrazolo[1,5-a]pyrimido[3,4-d]pyrimidine

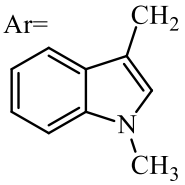
Saleh and co-workers[xxxi] synthesized linear benzo fused pyrazolopyrimidopyrimidines such as 2-[(N-methylindolyl)methyl]-*4H*-5-oxo-11-methylbenzo[*d*]pyrimidine [3',2':2,3]pyrazolo[5,4-*d*] pyrimidine **(55)** from respective 3-chloropyrazolopyrimidine **(54)** by the treatment with anthranilic acid and acetic anhydride (scheme 16).

Scheme 16



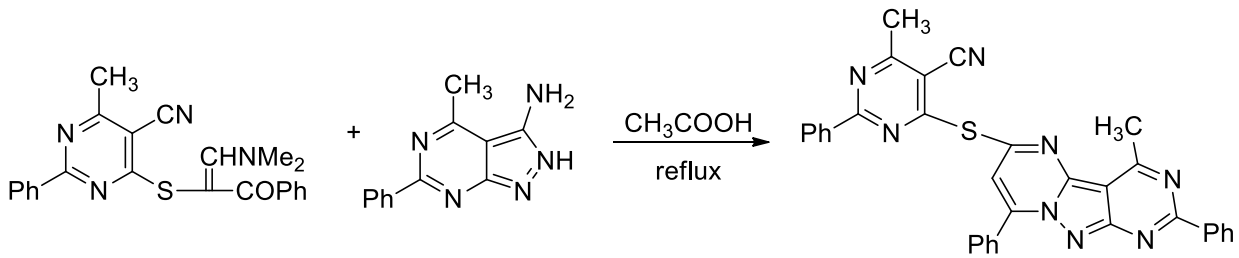
54 **55**

Where Ar=



4-(1-(Dimethylamino)-3-oxo-3-phenylprop-1-en-2-ylthio)-6-methyl-2-phenylpyrimidine-5-carbonitrile **(56)** was reacted with 3-aminopyrazolopyrimidine **(57)** in order to prepare pyrimido-[4′,5′:3,4]pyrazolo[1,5-*a*]pyrimidine **(58)**[xxxii] (scheme 17).

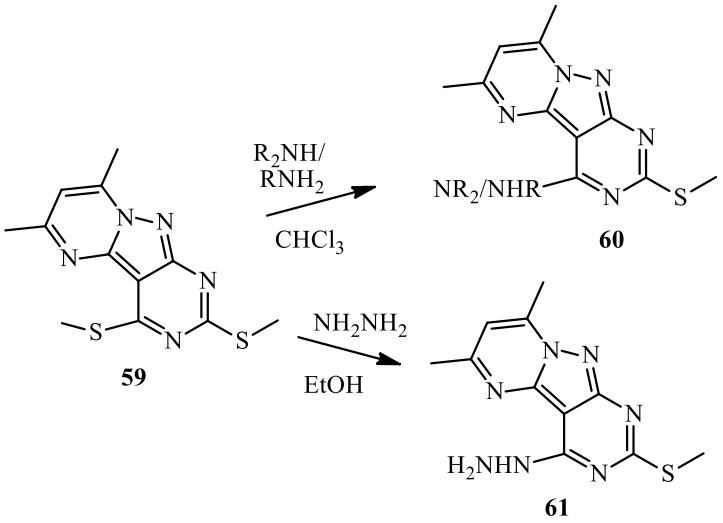
Scheme 17



56 **57** **58**

Selective amination was carried out in pyrazolopyrimidopyrimidines **(59)** using primary or secondary amines and hydrazine to give respective pyrazolopyrimidine derivatives **(60-61)**[xxxiii] (scheme 18).

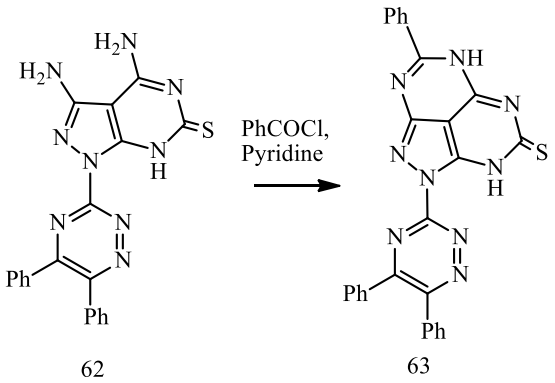
Scheme 18



1,2.4 Pyrazolo[5,4,3-*k*]pyrimdo[4,3-*d*]pyrimidine

Synthesis of pyrazolo[5,4,3-*k*]pyrimdo[4,3-*d*]pyrimidine **(63)** was carried out by Ali *et al*[xxxiv] from reaction between 3,4-diaminopyrazolo[3,4-*d*]pyrimidine **(62)** and benzoyl chloride in presence of pyridine under heating (scheme 19) and was reviewed by Rashad *et al*[xxxv].

Scheme 19



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CONCLUSIONS

In conclusion the structure, synthesis via different routes and several synthetic and biological applications of the known six types of pyrazolopyrimidopyrimidines have been stated since 1956. Pyrazolopyrimidopyrimidines depending on difference in fusion have been categorized as pyrazolo[3,4-*d*]pyrimido[1,6-a]pyrimidine, pyrazolo[1,5-*a*]pyrimido[4,5-d]pyrimidine, pyrazolo[4,3-*e*]pyrimido[1,2-*c*]pyrimidine, pyrazolo[1,5-*a*]pyrimido[5,4-*e*]pyrimidine, pyrazolo[1,5-*a*]pyrimido[3,4-*d'*]pyrimidine and pyrazolo[4,5,3-*k*]pyrimido[3,4-*d*]pyrimidine. Some pyrazolopyrimidopyrimidines found to be the efficient intermediate to prepare analgesic, antipyretic and anti-inflammatory agents. Some have been reported to possess anticancer, antimicrobial, analgesic, antipyretic and anti-inflammatory along with gastro protective activity. Some of them proved to be the useful for Parkinson's disease, depression, narcolepsy and preventing damage to cognitive function. As a result, this review covering

some periods from 1956 to 2022 has been prepared to discuss some of the structural pathways of pyrazolopyrimidopyrimidine compounds as well as some of their interactions and applications.

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