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AN INSIGHT INTO THE SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRAZOLOQUINOLINES

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ABSTRACT

Sydnones and their derivatives show a variety of pharmacological properties and hence have been proved to be useful in the search for new therapeutic agents. These properties have motivated researchers to investigate novel derivatives with improved biological activity and diverse applications. Sydnones undergo cycloaddition reaction to give pyrazoles. The broad spectrum of pharmacological activity of pyrazoles indicates that these compounds undoubtedly are of considerable interest. Sydnones fused with pyrazoles, namely, pyrazoloquinolines are a widely studied group of molecules due to their biological activities. The current review is an attempt to consolidate the strategies used for the synthesis of biologically active sydnones and their derivatives, namely pyrazoles and pyrazoloquinolines. The evaluation of their biological activities have also be discussed.

Keywords- *anticancer, antiinflammatory, anticonvulsant, pyrazoloquinolines, sydnones, sydnoquinoline etc.*

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INTRODUCTION

Compounds of the mesoionic class have interesting structural features due to their betain-like character. They consist of a five membered ring associated with a sextet of *p* and Π electrons supported by a partial positive charge in the heterocyclic ring counterbalanced by a formal negative charge. These compounds exhibit ionic resonance structures due to their planar aromatic character, their relatively small size and variation in electron density around the ring. The association of these characteristics suggests a high probability of strong interactions with biomolecules such as DNA and/or proteins. Sydnones belong to this class of compounds, namely mesoionic compounds. Chemically, sydnones are 1, 2, 3-oxadiazolium-5-olates [1]. A large number of sydnone derivatives have been synthesized [2-4] and reported to possess a wide spectrum of biological activities such as antiviral, antimicrobial, antiinflammatory, analgesic, anthelmintic [5], antitumor [6], free radical scavenging [7] and nitric oxide donor [8] activity. The stimulant drugs, Feprosidine and Mesocarb, are substructures of sydnones imine in which the keto group of sydnones (=O) is replaced by the imino group (=NH). Apart from their biological activity, another attractive feature of sydnones is their application as synthetic

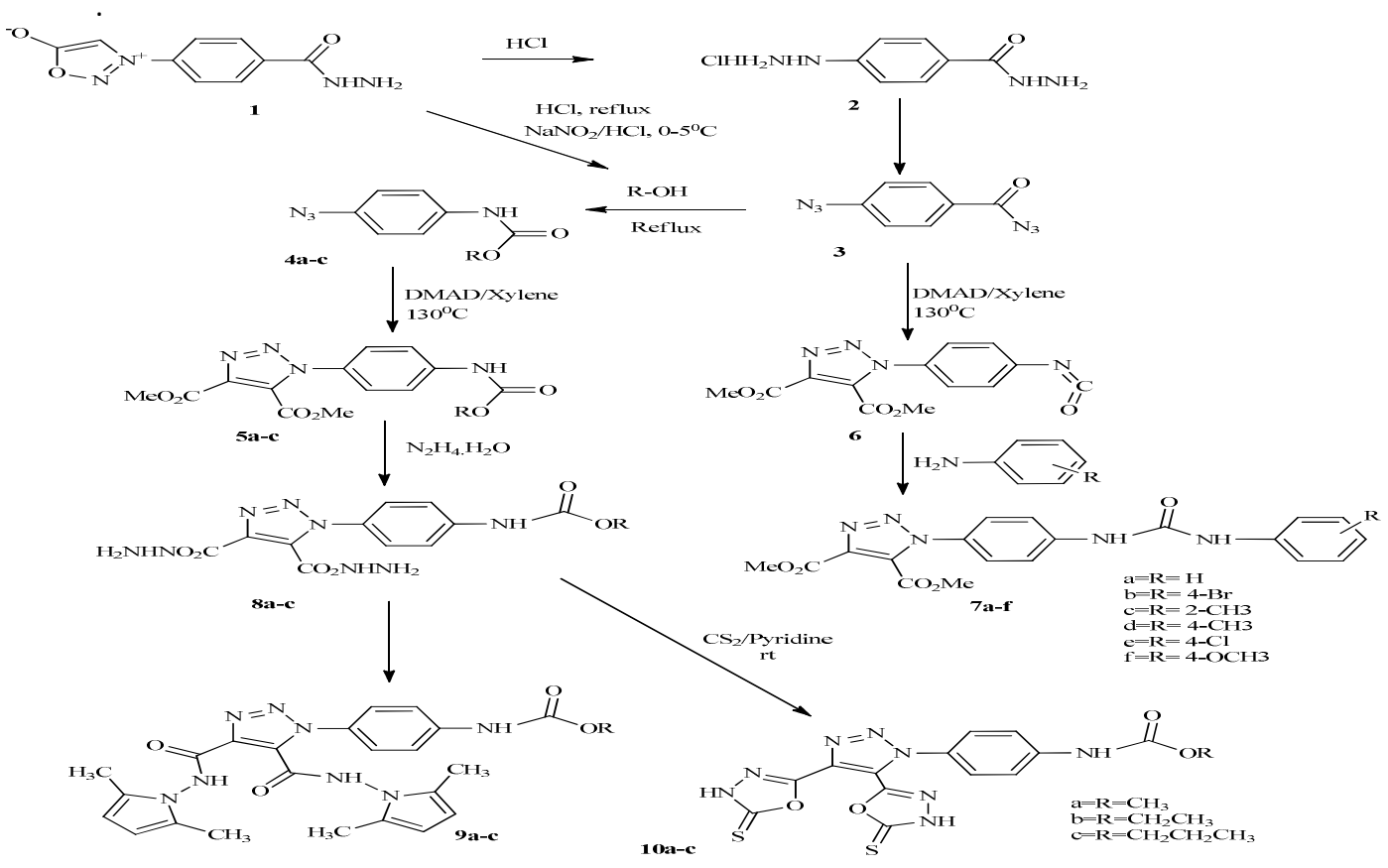
precursors for other molecules like pyrazolines and pyrazoles.

Pyrazoles and their derivatives have gained considerable importance over the years due to their wide range of biological activities like antibacterial [9], anticancer[10], antiinflammatory [11], antitumor [12], anticonvulsant [13], *etc.* Pyrazoloquinolines, quinolines fused to pyrazoles, have been reported to possess anticancer [14], antipsychotic[15] and antiviral activity among others.

In the present article, we have made an attempt to review the synthesis, pharmacological properties and structure-activity relationships of sydnoquinolines and pyrazoloquinolines including some of the related patents for the period 1985-2013.

Sydnones as synthons for other biologically active molecules

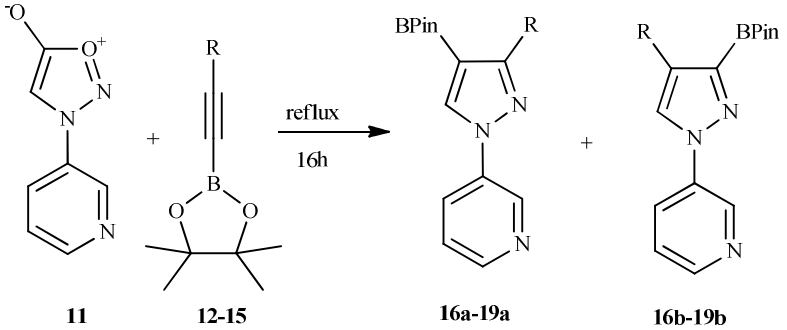
Latthe *et al.,*[16] have reported the synthesis of 1,2-diaza-five membered heterocyclic systems. They synthesized 4-(hydrazinocarbonyl)phenylhydrazine **2** and used it as a synthon for the synthesis of bismesoionic compounds (**Scheme 1**). The synthesized molecules were then evaluated for their antibacterial activity. They reported the synthetic utility of the bisfunctional compound, for the synthesis of novel bis azide–4-(azidocarbonyl)phenyl azides **3**, that were a synthetic challenge till then. The azides were then used for the synthesis of compounds **9a-c** and **10a-c**. These compounds were found to show moderate antibacterial activity. All the phenylcarbamates **5a-c** showed considerably good antifungal activity when compared to the standard, griseofulvin.

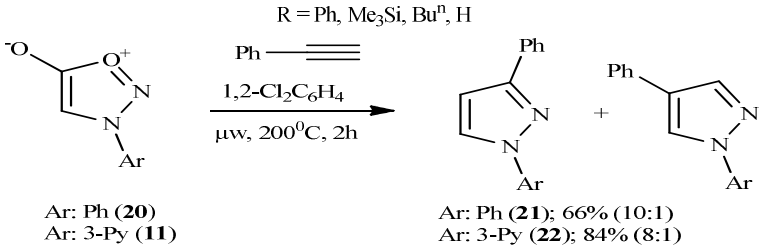


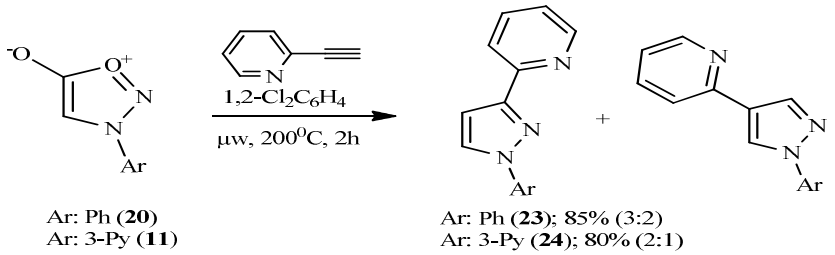
Scheme 1

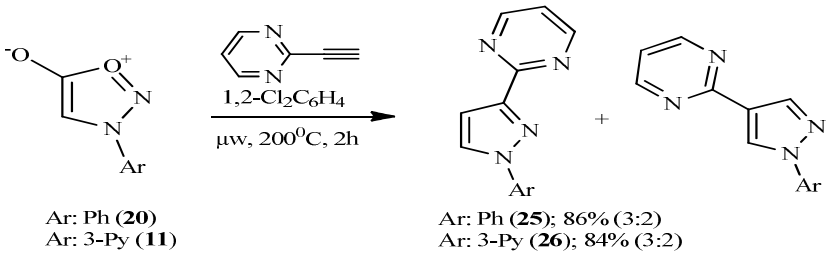
Foster *et al.,*[17] have synthesized azine-substituted pyrazoles *via* the cycloaddition of sydnones (**Scheme 2**). This synthesis is novel as not many *N*-azine-substituted sydnones have been reported in literature. The authors studied the cycloaddition of sydnones with alkylboronates for

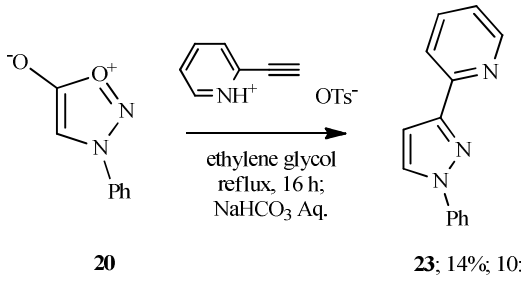
the synthesis of pyrazole boronic acid derivatives **16-19**. These studies are of importance due the the boronate motif. The authors have thus efficiently demonstrated that alkyne/sydnone cycloaddition reactions are a direct and convenient method for the preparation of azine-substituted pyrazoles.

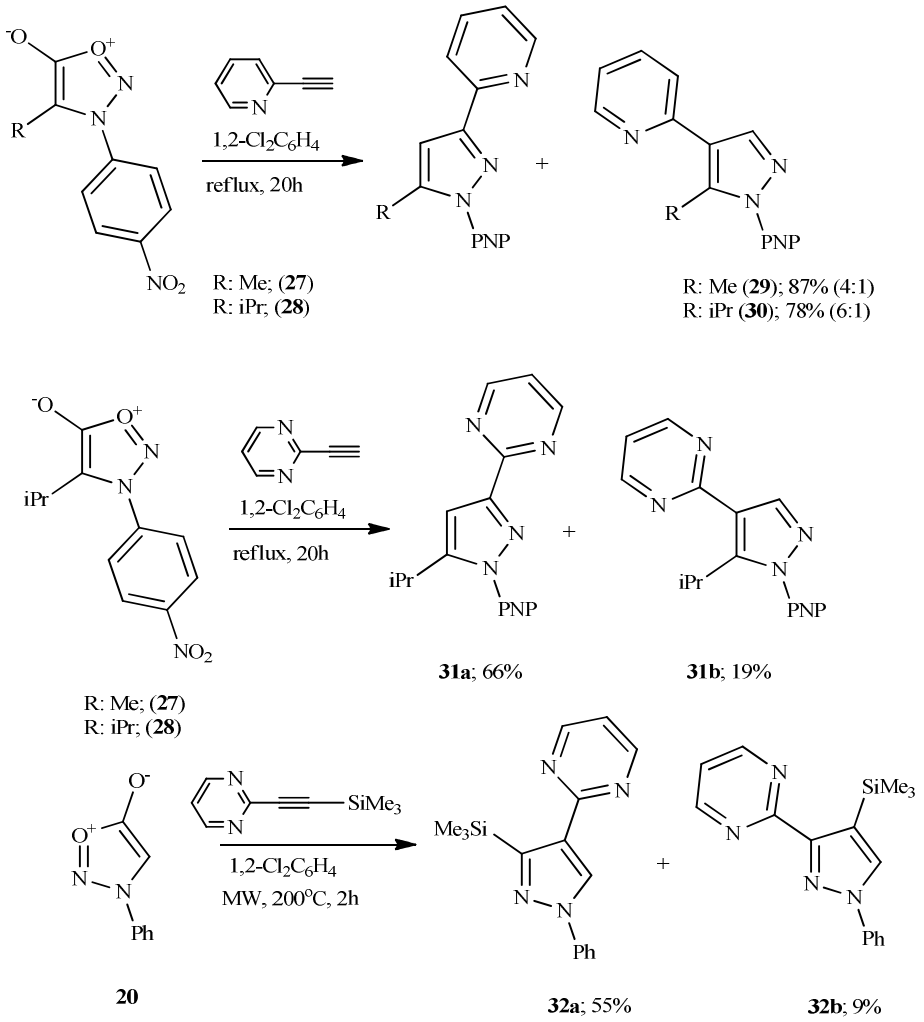






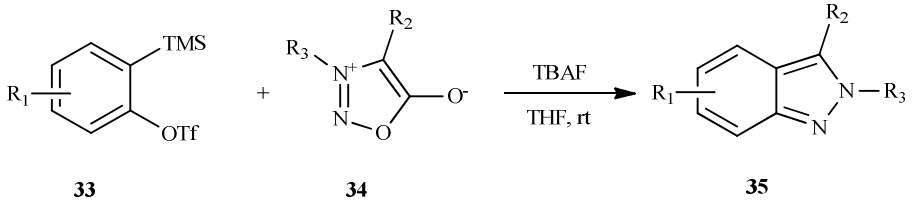






Scheme 2

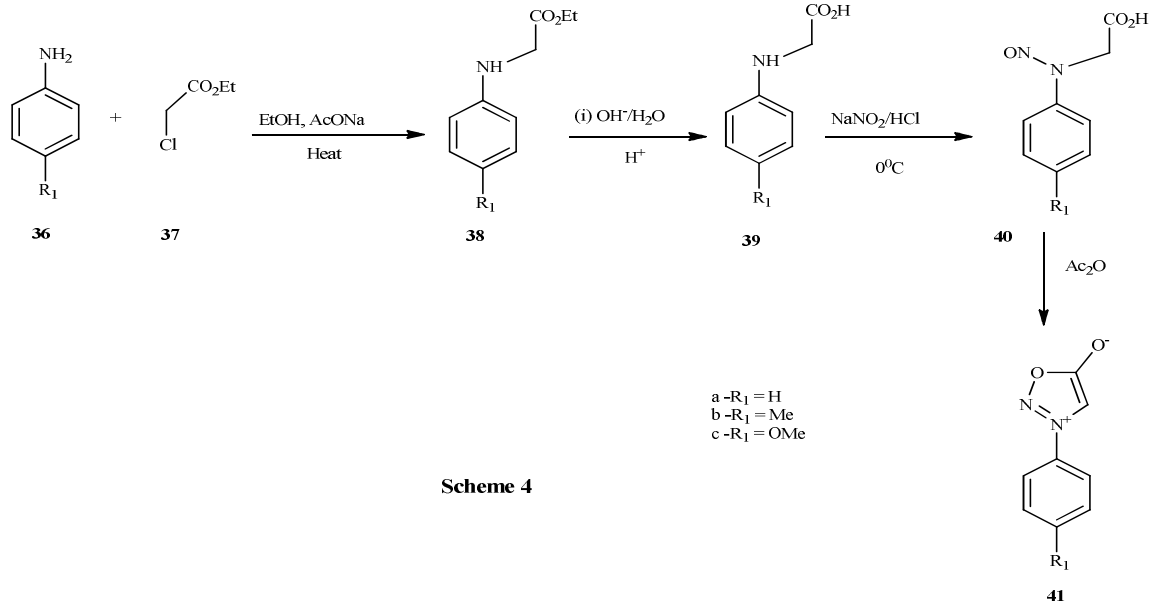
Wu *et al.,*[18] have reported the synthesis of 2H-indazoles *via* the [3+2] cycloaddition of arynes to sydnones (**Scheme 3**). They carried out the cycloaddition reaction with different precursors of arynes and observed that the reaction proceeded to completion with good yields with single products **35**. The reaction conditions were mild. A detailed study on the mechanism required was also in progress by the authors.



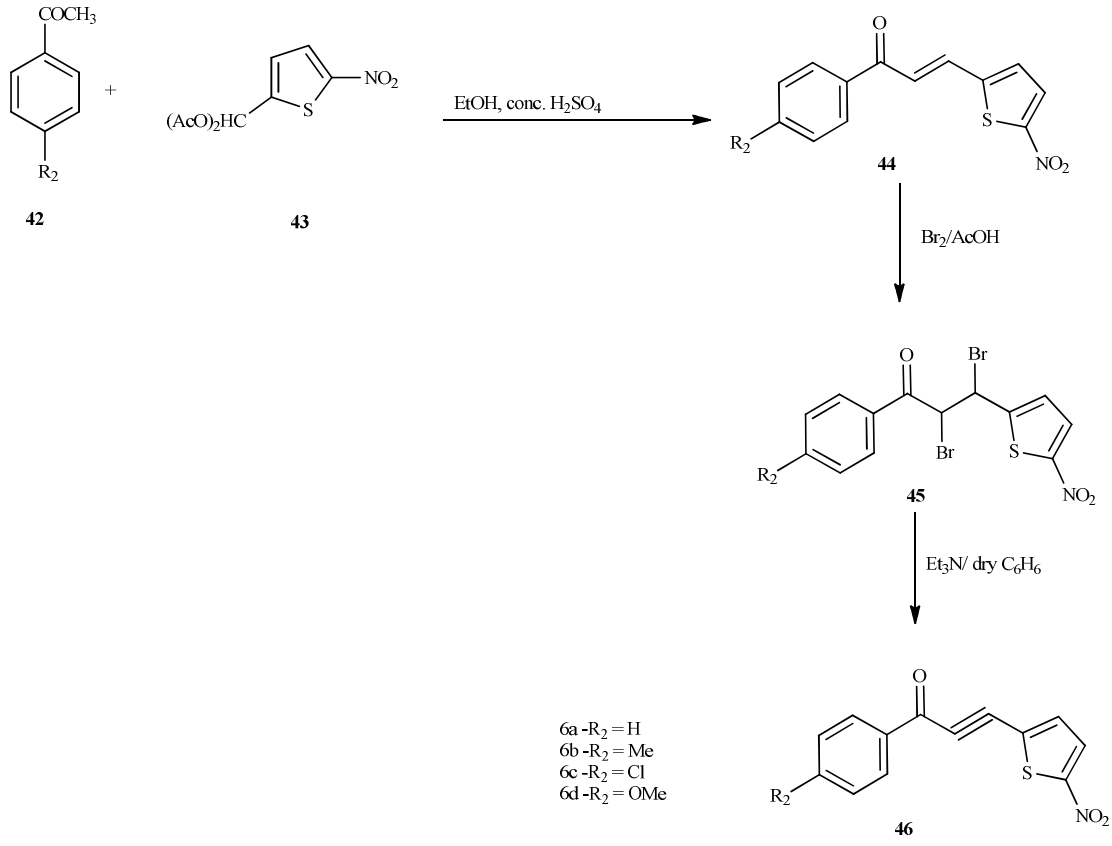
Scheme 3

Sateesha Rai *et.al.,*[19] have synthesized a series of novel 1-aryl-3-(5-nitro-2-thienyl)-4-aroyl-pyrazoles **49** (**Scheme 6**)*via* 1,3-dipolar cycloaddition of 3-arylsydnones **41** (**Scheme 4**) with 1-aryl-3-(5-nitro-2-thienyl)-2-propyn-1-ones **46 (Scheme 5)**. The synthesized molecules were evaluated for their antibacterial (*Escherichia coli* ATCC-25922, *Staphylococcus aureus* ATCC-25923, *Pseudomonas aeruginosa* ATCC-27853, recultured *Bacillus subtilis*) and antifungal activity [(*Candida albicans*

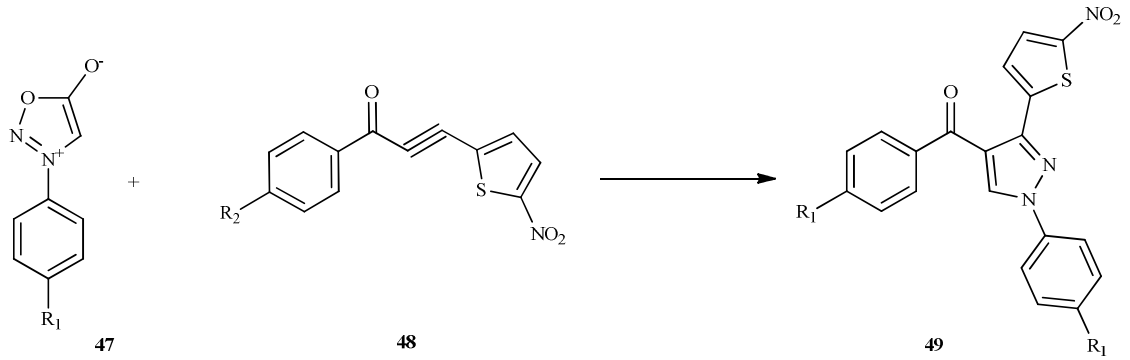
(NCIM No. 3100)] by serial dilution method. In an attempt to increase the activity of the molecules they introduced 5-nitrofuran and 5-nitrothiophene moiety. The results revealed that some of the tested compounds had good activity. The compounds with methyl and chloro derivatives were found to show excellent antibacerial activity. The compounds with methyl, chloro and methoxy substituents were found to show exceptionally good antifungal activity when compared to the standard, fluconazole.



Scheme 4

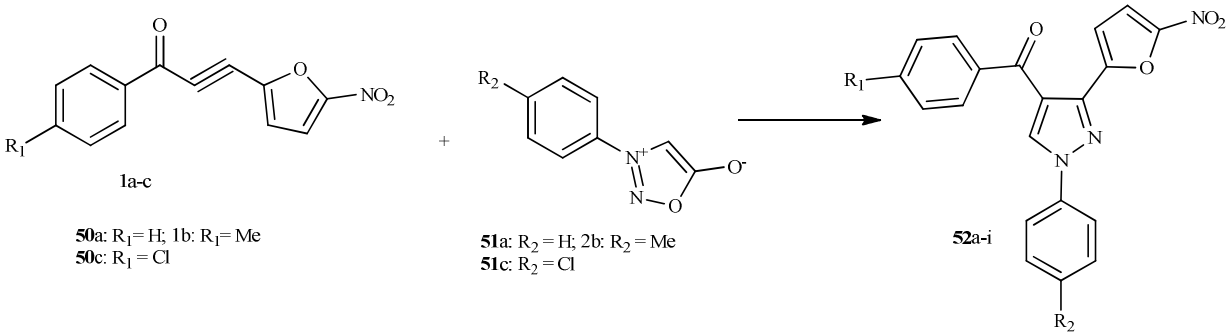


Scheme 5



Scheme 6

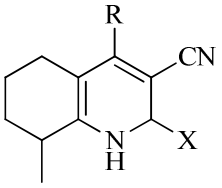
Ganesha Rai *et al.,*[20] have synthesized a series of 1-aryl-3-(5-nitro-2-furyl)-4-aroylpyrazoles **52** via 1,3-dipolar cycloaddition reaction of 3-arylsydnones **51** and *α,β*-acetylenic ketones **50** containing nitrofuran moiety (**Scheme 7**). Although 1,3-dipolar cycloaddition of sydnones is well known and well studied, the authors felt that less attention has been given to the regiochemistry of 1,3-dipolar cycloaddition reaction with more complex dipolarophiles like 1-aryl-3-(5-nitro-2-furyl)propynones **50**. They found that the reaction of these dipolarophiles with 3-arylsydnones resulted in regiospecific 1-aryl-3-(5-nitro-2-furyl)-4-aroylpyrazoles in good yields. In order to study the regiospecificity in more detail the authors used different para substituted aryl compounds and in all the cases the reactions were found to be highly regioselective. They found the formation of single products and this was confirmed using X-ray crystallographic studies.



Scheme 7

Chemistry and Pharmacology of Pyrazoloquinoline derivatives.

Faidallah *et al.,*[21] have studied the DNA binding property of tetrahydroquinolines **53**, tetrahydropyrimidino[4,5-*b*]quinolines **54** and tetrahydropentaazacyclopenta[*a*]anthracenes **55**. All the synthesized compounds displayed good antitumor activity and good DNA binding activity. Tricyclic tetrahydropyrimidino [4,5-*b*]quinolines, however, showed better activity.



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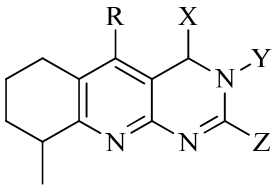

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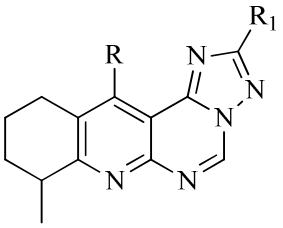

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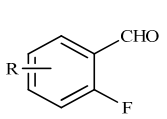
Jun Ya Kato *et al*.,[22] have reported a novel method for the synthesis of pyrazolo[1,5-*a*]quinolines **58** under transition metal free conditions (**Scheme 8**). This method involved the synthesis of pyrazoloquinolines *via* a combination of aromatic nucleophilic substitution and knovenagel condensation.



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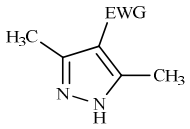

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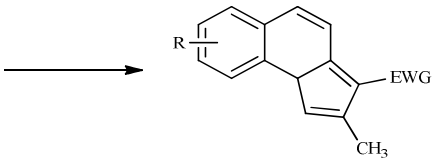

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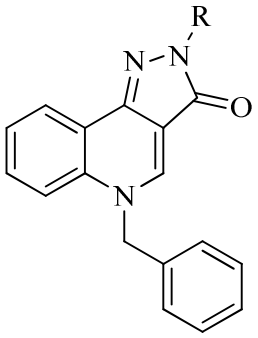
EWG = CO_2Et, CN, Br

Scheme 8

Mishra [23] has studied the 2D- structure-activity relationship (QSAR) of 2,5-dihydropyrazolo[4,3-*c*]quinolines on the inhibition of phosphodiesterase-4 (PDE-4). The models were checked for the observed biological activity and the predicted activity. The biological activities of the selected compounds were shown to be due to the hydrophobicity, electrostatic and topological properties of the molecules. The authors concluded that the increase PDE-4 inhibitory activity of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one derivatives was due to the presence of groups contributing to flexibility in chain length and lipophilicity of molecule.



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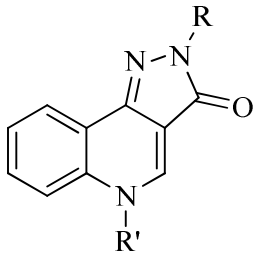

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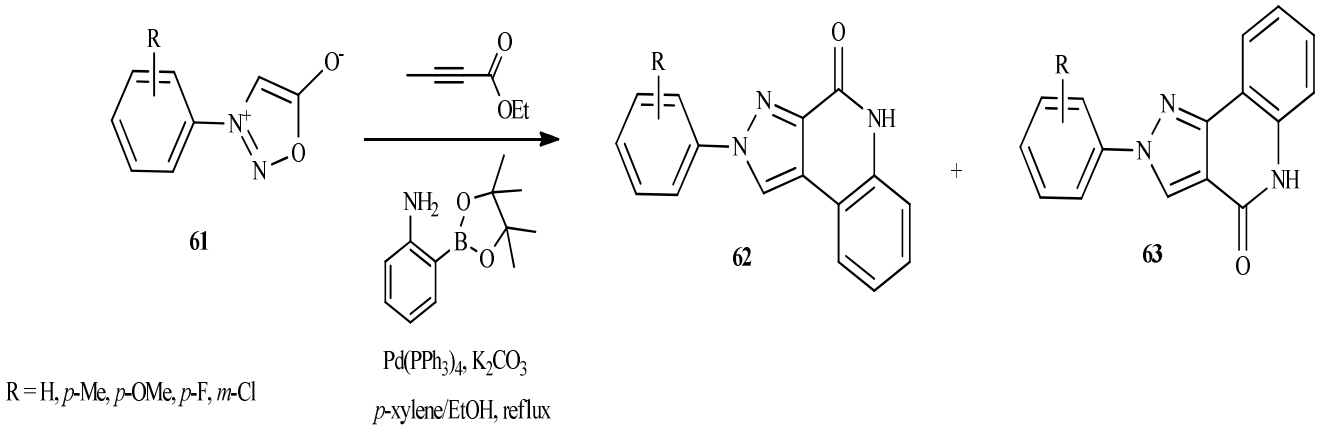
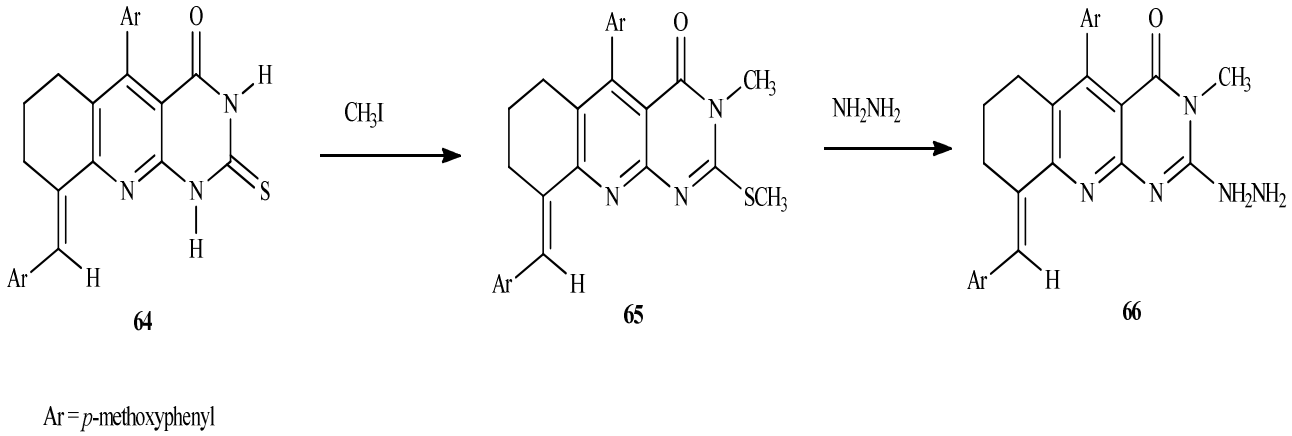
Chang *et al.,*[24] have efficiently synthesized two regioisomers of 2-arylpyrazolo[3,4-*c*]quinolin-4(5H)-ones **62** and 2-arylpyrazolo[4,3-c]quinolin-4(5H)-ones **63** from 3-arylsydnones **61**, ethyl 3-bromopropynoate, and 2-aminophenylboronic acid pinacol ester using $Pd(PPh_3)_4$ as catalyst (**Scheme 9**). This efficient one-pot synthesis methodology involved 1,3-dipolar cycloaddition, Suzuki coupling reaction and intramolecular cyclization.



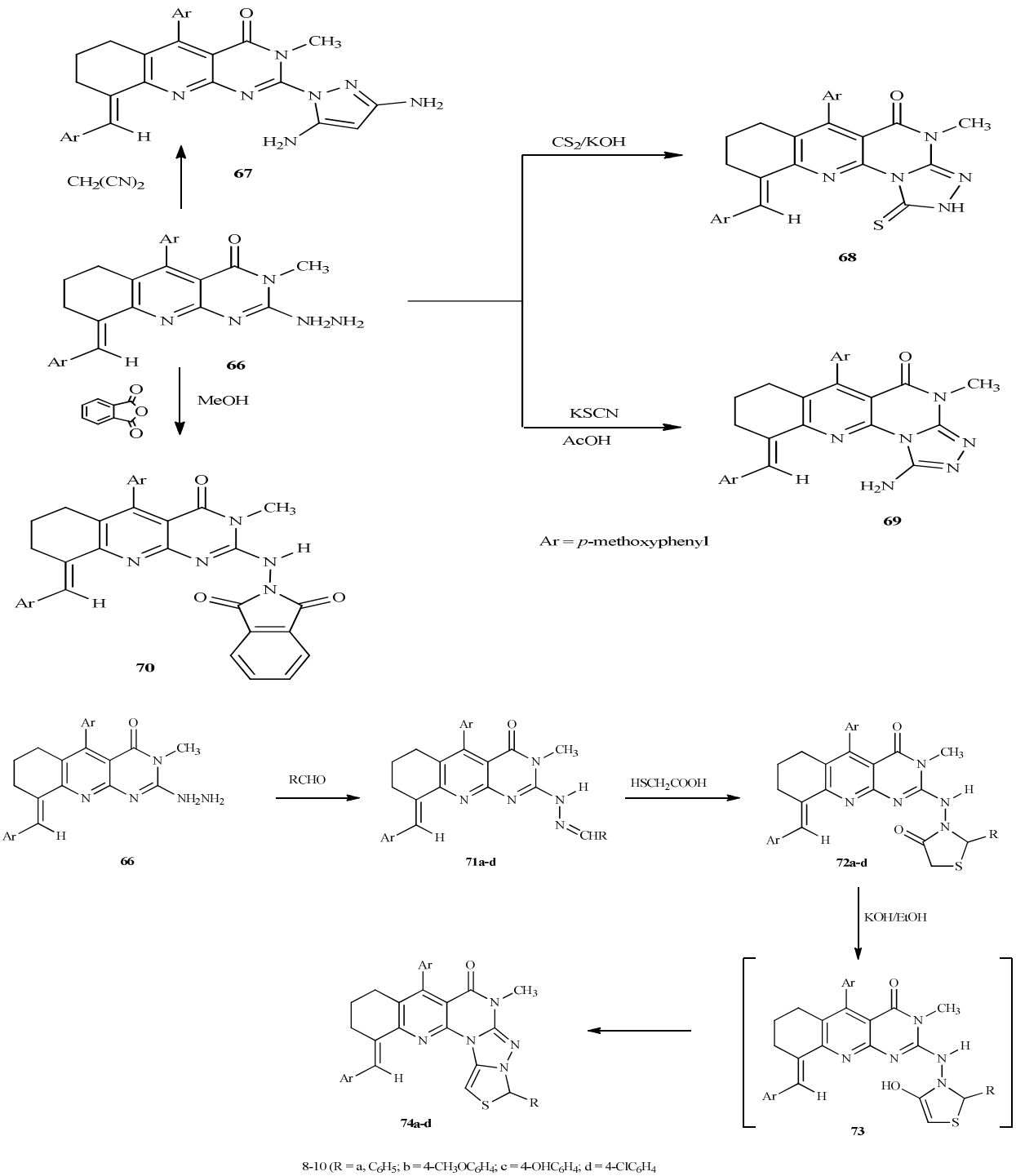
Scheme 9

Abu-Hashem *et al.,*[25] have synthesized a series of 2-hydrazinyltetrahydropyrimido[4,5-b]quinolin-4(3H)-ones **66** by desulphurization of S- and N-dimethyl derivatives **65** with hydrazine hydrate (**Scheme 10**).



Scheme 10

These molecules on reacting further with malonitrile, carbondisulphide, potassium thiocyanate, pthalic achydride and aromatic aldehydes gave 3,5-di aminopyrazolopyrimido[4,5-b]quinolines **67**, triazolotetrahydropyrimido[4,5-b]quinolines **68**, aminotriazolopyrimido[4,5-b]quinolines **69**, aminopthalimidopyrimido[4,5-b]quinolines **70** and *N*-arylidene hydrazinepyrimido[4,5-b]quinoline derivatives, respectively **74** (**Scheme 11**). The synthesized molecules were evaluated for their antitumor potential and a few of them proved to be potent antitumor agents.

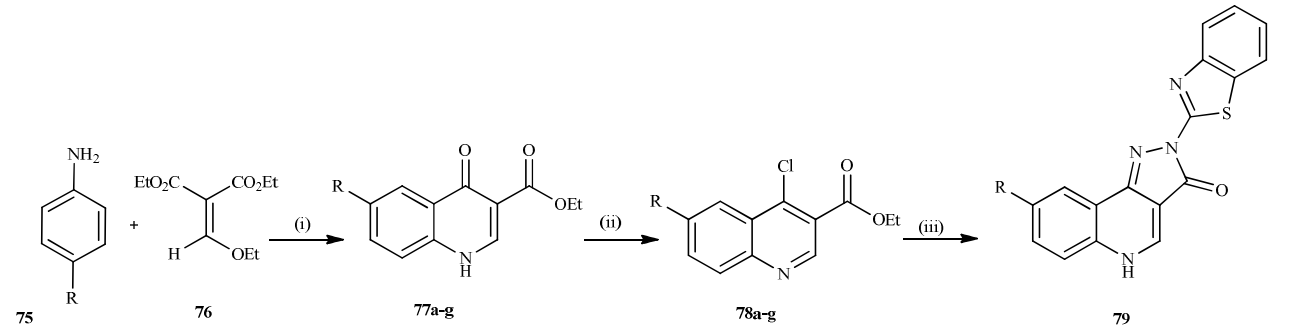


Scheme 11

The *in vitro* cytotoxicity studies of the synthesized molecules revealed that the pyrimidoquinoline when introduced into the basic scaffold helped improve the antitumor activity. Compounds **67, 68, 69** and **74d** showed cytotoxicity against KB, MGC-803 and MCF-7 cell lines and compound **67** showed potent cytotoxicity against CNE2 cancer cell lines.

The structure-activity relationship revealed that the presence of 3,5-diaminopyrazolo, 2-amino-1,3,4-triazolo, 1,3,4-triazolo and triazolothiazolidine moieties linked to the pyrimido[4,5-b]quinolines enhanced the cytotoxicity of the molecules.

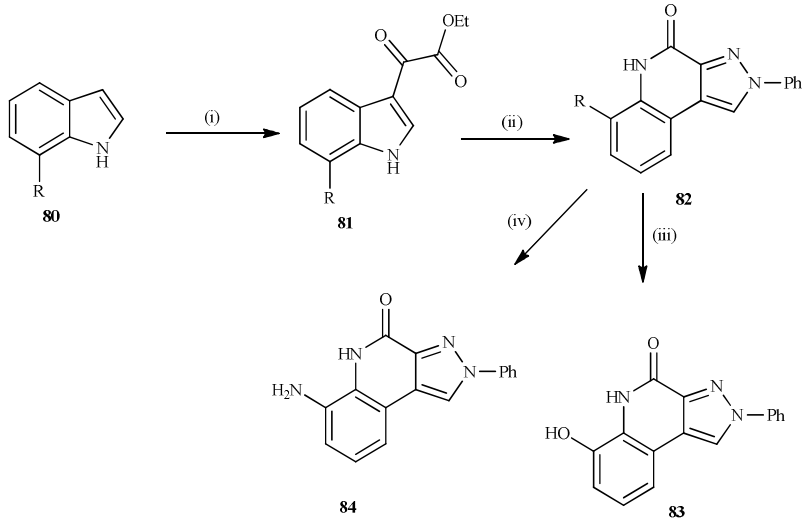
Reis *et al.,*[26] have synthesized and evaluated some novel 2-(benzo[d]thiazol-2-yl)-8-substituted-2H-pyrazolo[4,3-c]quinolin-3(5H)-ones **79** (**Scheme 12**) for their anticancer activity against MDA-MB-435, HL-60, HCT-8 and SF-295 cell lines. The results revealed that compounds **79b** and **79c** exhibited good anticancer activity on all three cell lines with IC_{50} values less than 5µg/mL. Molecular modeling studies were also carried out by these authors using Osiris programs to evaluate the electronic properties, hydrogen bonding, molecular weight and theoretical toxicity properties.

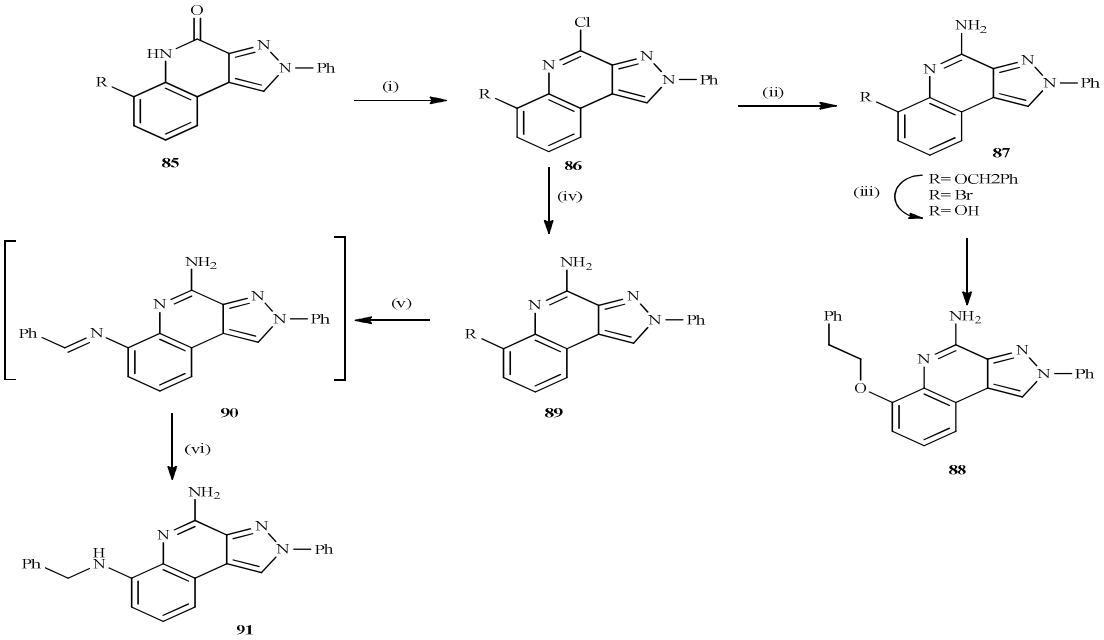


Scheme 12

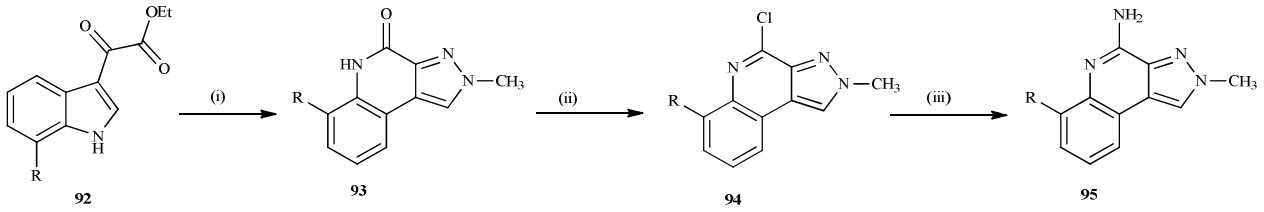
Hemolytic assay studies revealed that none of the molecules were capable of causing hemolysis in mouse erythrocytes even at high concentrations.

Lenzi *et al.,*[27] have designed and synthesized 2-phenyl and 2-methylpyrazolo[3,4-c]quinolines-4-one **83 , 84** (**Scheme 13**) and 4-amine derivatives **91, 95** (**Scheme 14**) as adenosine receptor antagonists. The synthesized molecules were evaluated for their ability to displace specific [3H]DPCPX, [3H]ZM241385 and [125I]AB-MECA binding from cloned hA1, hA2A and hA3 receptors, respectively. The results revealed that the synthesized molecules showed A_1 receptor affinity and selectivity. Molecular docking studies were also carried out in order to define the structural features of the binding (pdb code: 3EML). The docking studies revealed that the introduction of the functional group at the 6th position leads to enhanced affinity towards the A1 receptor and also selectivity.



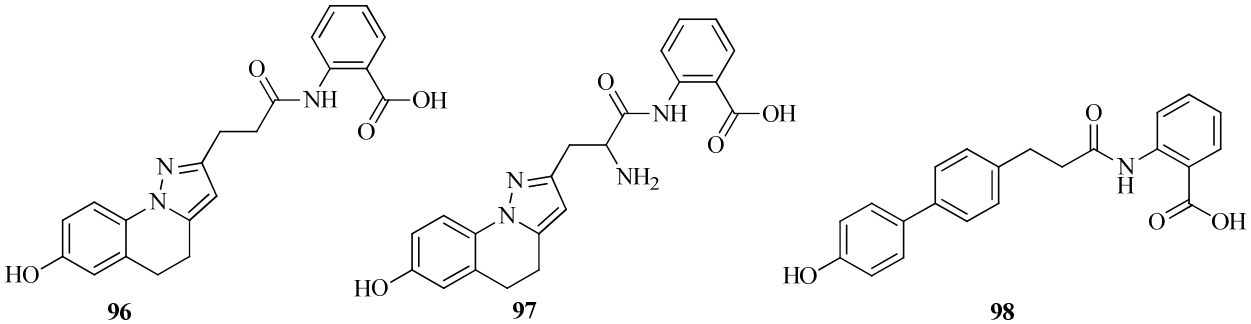


Scheme 13



Scheme 14

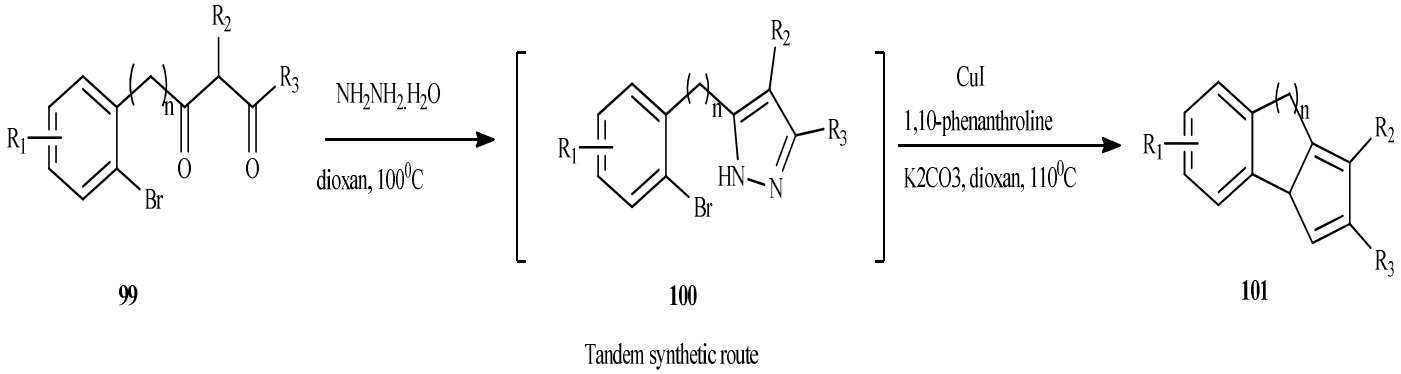
Imbriglio *et al.,*[28] have worked on a series of amino-anthranilic acid derivatives as a new class of low serum-shifted high affinity full agonists of the human orphan G-protein-coupled receptor, GPR109a, with improved ADME profile. They designed a series of GPR109a receptor antagonists. A few pyrazoloquinolines based on these series of compounds were found to show a 10-fold reduction of the serum shift.



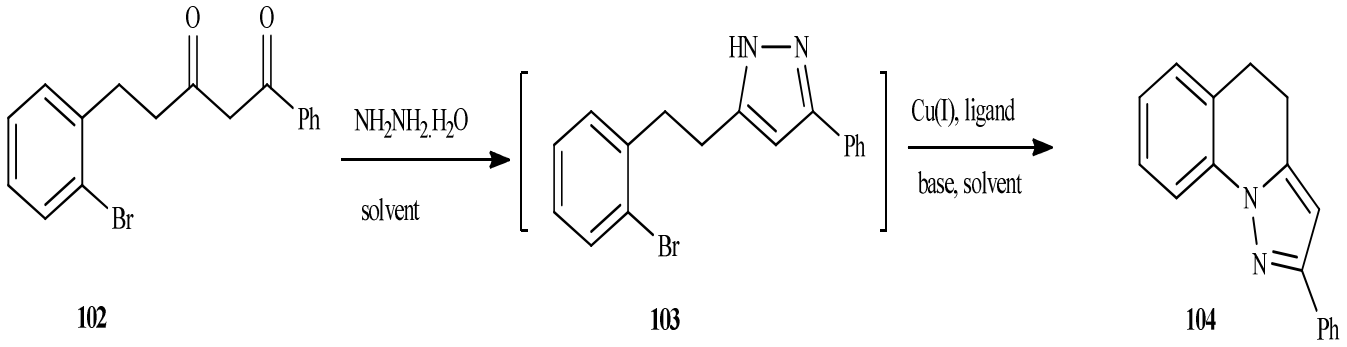
96 **97** **98**

The anthranilic acid derivatives were found to have a 10,000 fold shift of serum-potency, excellent *in vitro* profile and modest ADME properties. Considering the importance of the anthranilic acid moiety and the terminal phenol group they designed molecules keeping these two moieties intact and modifying the rest of the molecule in order to increase the efficacy. They successfully synthesized a new class of aminoanthranilic acid agonists of GPR109a with potent agonists, reduced serum shift and excellent ADME properties.

Hang *et al.,*[29] have carried out a facile copper catalyzed tandem reaction for the synthesis of 4,5-dihydropyrazolo[1,5-a]quinoline **104** (**Scheme 16**) and pyrazolo[1,5-a]indoles **101 (Scheme 15**). They found that the yields pyrazolo[1,5-a]quinolines were found to be better than the indoles. This was explained on the basis of the steric hinderance. They also came up with an efficient method for the synthesis of some fused ring indoles and pyrazoles.

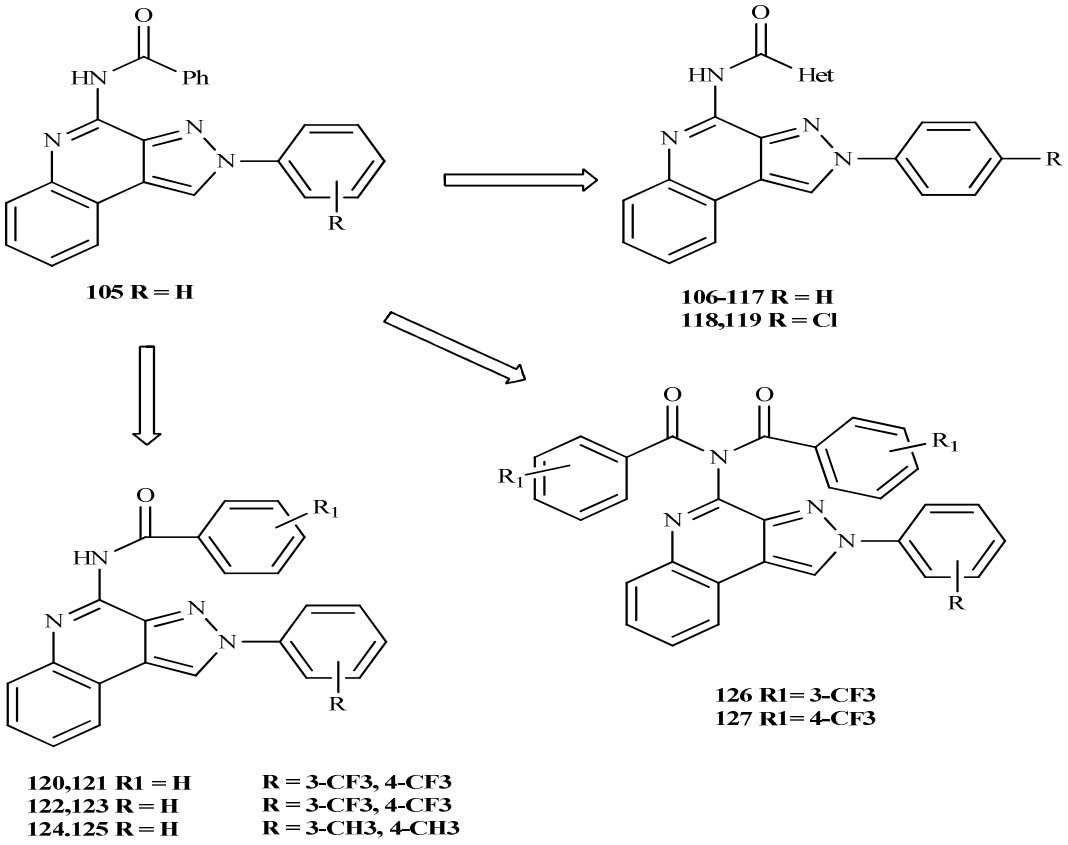


Scheme 15

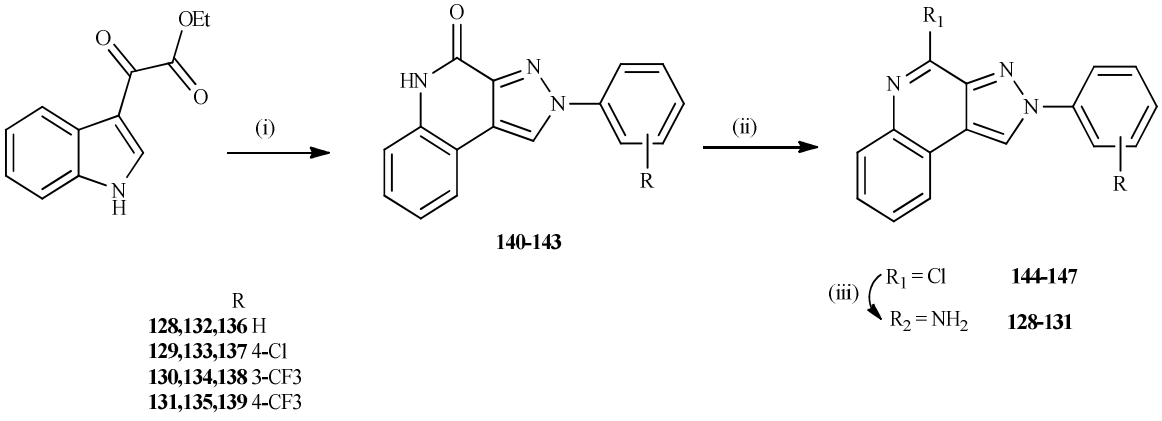


Scheme 16

Colotta *et al.,*[44] have reported a series of pyrazoloquinolines (**Scheme 17**) and found them to exhibit a high affinity for adenosine receptors and were active in nanomolar quantities.

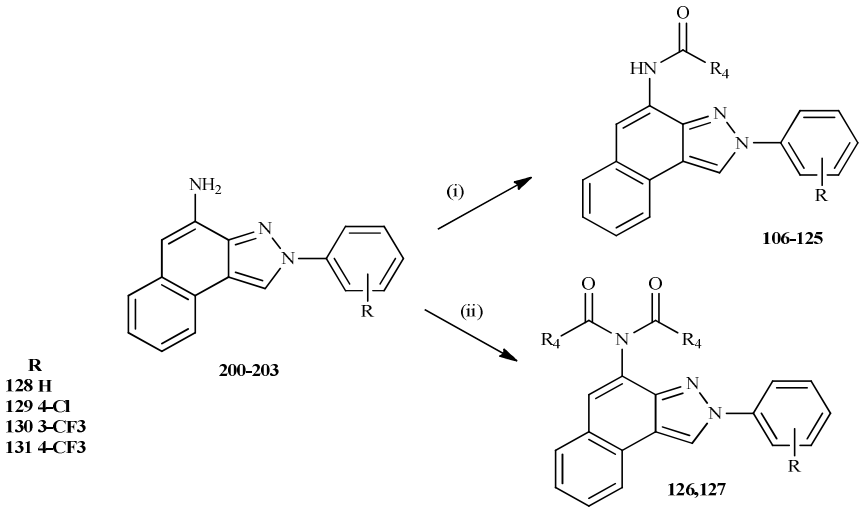


Scheme 17



(i) arylhydrazine hydrochloride, absolute EtOH, AcOH, microwave irradiation; (ii) $PCl_5/POCl_3$; (iii) $NH_3(g)$, absolute EtOH.

Scheme 18



	R_4	R		R_4	R
106	2-furyl	H	117	2-pyrazinyl	H
107	3-furyl	H	118	4-pyridyl	Cl
108	2-(5-methylfuryl)	H	119	2-furyl	Cl
109	2-thienyl	H	120	C_6H_5	3-CF3
110	3-thienyl	H	121	C_6H_5	4-CF3
111	4-thiazolyl	H	122	C_6H_4-3-CF_3	H
112	2-pyridyl	H	123	C_6H_4-4-CF_3	H
113	3-pyridyl	H	124	C_6H_4-3-CH_3	H
114	4-pyridyl	H	125	C_6H_4-4-CH_3	H
115	2-pyrimidyl	H	126	C_6H_4-3-CF_3	H
116	4-pyrimidyl	H	127	C_6H_4-4-CF_3	H

(i) Suitable carboxylic acid, 1-hydroxybenzotriazole, NEt3,4-(dimethylamino)pyridine,1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride,DMF; (ii) ArCOCl, anhydrous pyridine, methylene chloride.

Scheme 19

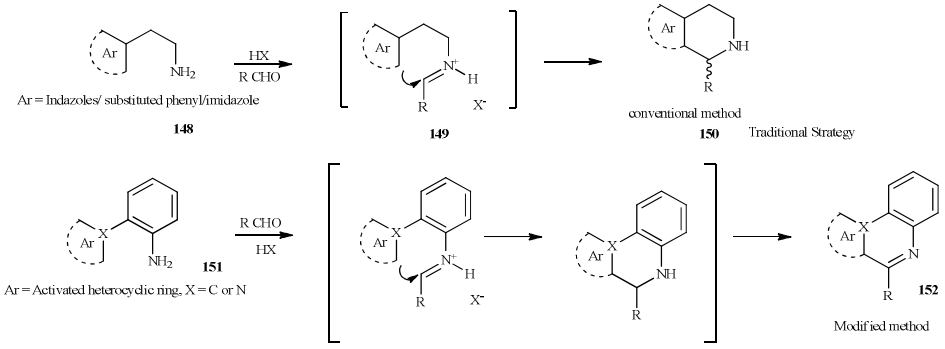
The target compounds were synthesized from 2-arylpyrazolo-[3,4-*c*]quinolines-4-amines, **128-131** (**Scheme 18, 19**), which were prepared from 3-ethoxalylindole. The final molecules **106-125**, **126** and **127** were synthesized from 4-amino derivatives by reacting with suitable carboxylic acid in DMF in the presence of 1- hydroxybenzotriazole, triethylamine, and 4-(dimethylamino)pyridine. 4-Diaroylamino derivatives, **126** and **127**, were obtained by refluxing the 4-amino derivative, **128,** with an excess of 3-trifluoromethylbenzoyl chloride and 4-trifluoromethylbenzoyl chloride, respectively, in anhydrous methylene chloride and pyridine.

The structure-activity relationship of the synthesized compounds revealed that introducing aroyl ring in place of the benzoyl moiety increases the binding affinity of the synthesized molecules. They also evaluated the effect of various heterocyclic rings in the basic scaffold and found that the 2-furyl and 2- or 3- or 4-pyridyl rings were the most beneficial. The introduction of a methyl group to the furyl moiety increased the affinity further. The presence of a Me or OMe, either in the *para* or *meta* position, while maintaining a high hA3 affinity, reduced the hA3 versus hA1 selectivity. The authors also carried out the docking studies in order to obtain a structure based pharmacophore model (PDB id: 1L9H). The docking

scores were compared with the binding assay results. Based on these results a pharmacophore model was developed which may be of help in designing molecules for this receptor.

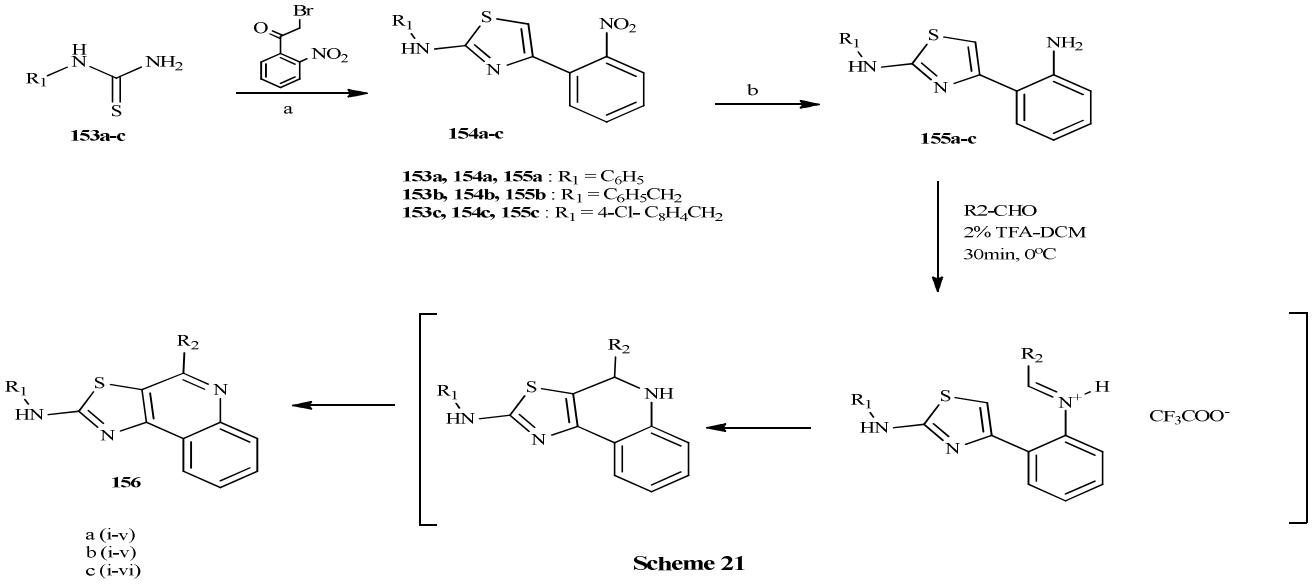
The authors have also reported a novel group of compounds as adenosine receptor antagonists, efficiently correlated the *in silico* and *in vitro* studies and explained the structure-activity relationships of the synthesized molecules.

Duggineni *et al.,*[30] have reported a novel application of a pictet Spengler reaction for the synthesis of some pyrazoloquinolines and thiazoloquinolines (**Scheme 20**). Thiazole and pyrazole based arylamine substrates were used for the reaction unlike the conventional method. The studies carried out by this group proved that arylamines linked to an activated heterocyclic ring can lead to a variety of second-generation substrates for the Pictet–Spengler cyclisation (**Scheme 21, 22**).

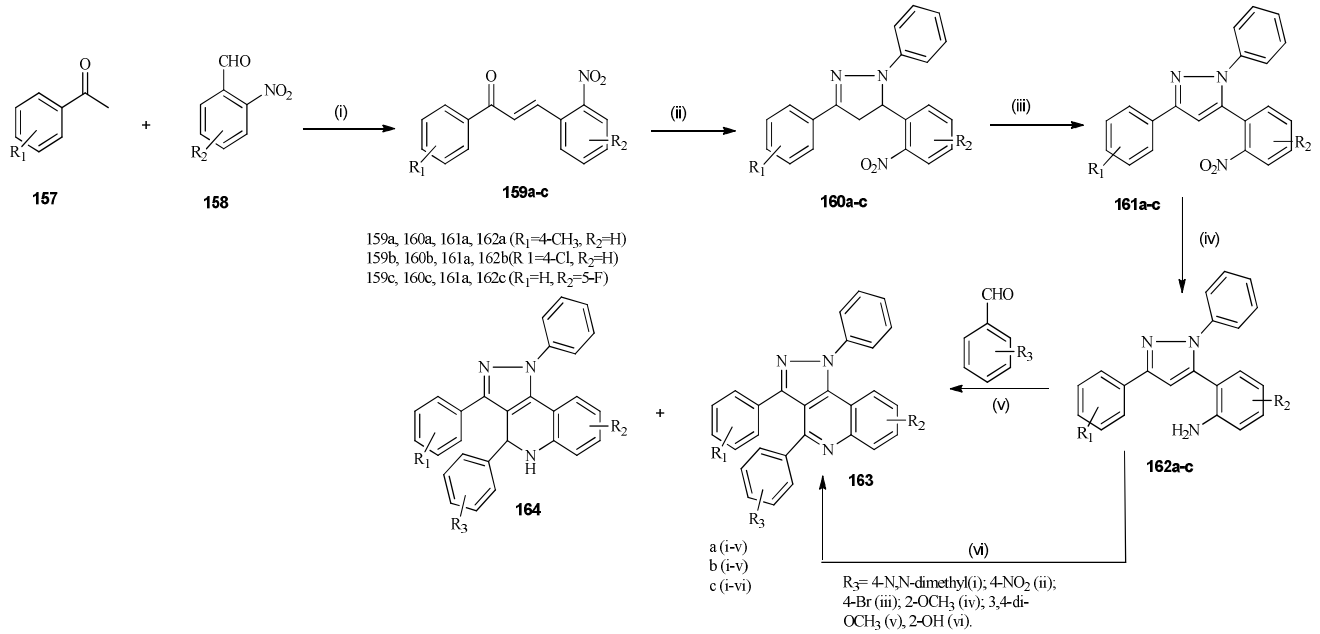


Scheme 20

The authors worked on this concept with the hope to synthesize benzannulated heterosystems and avoid the stereochemical issues associated with the traditionally used pictet Spengler reactions. Their work helped to prove that aryl amine derived substrates are likely to undergo pictet Spengler reaction faster than the substrate derived from aliphatic amines. They also worked out an efficient synthetic strategy for the synthesis of dihydropyrazoles (pyrazolines) and also successfully modified the problem faced during cyclisation when an electron withdrawing group is attached to the aldehyde.



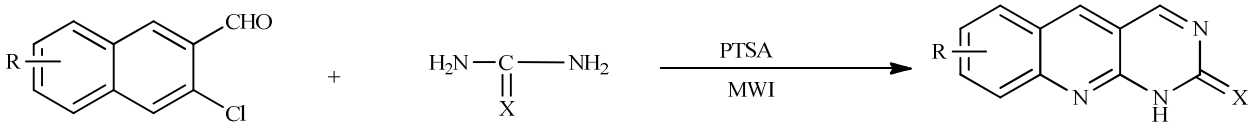
Scheme 21



Pictet–Spengler reaction using 2-(2,5-diphenyl-2H-pyrazol-3-yl)-phenylamine (4); conditions: (i) NH_4OAc, toluene, reflux, 7 h; (ii) phenyl hydrazine, EtOH, reflux 7 h; (iii) DDQ, DCM–THF ($1/_1$), rt, 4 h; (iv) $SnCl_2.2H_2O$, EtOH, reflux, 1.5 h; (v) p-TsOH, toluene, reflux, 4 h; (iv) p-TsOH, toluene reflux 4 h and DDQ, DCM–THF ($1/_1$), rt, 2 h.

Scheme 22

Selvi *et al.,*[31] have synthesized a series of pyrimido[4,5-*b*] **167, 168 (Scheme 22)** and pyrazolo[3,4-*b*]quinolines (**Scheme 24,25**) and evaluated them for their antimicrobial activity. They carried out the synthesis using environmentally benign solvent-free conditions using p-tolylsulphonic acid as catalyst and found that compounds **167a-g** and **168a-g** had significant effect on the inhibition of *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, compounds **167a–g** exhibited good antifungal activity against *Candida albicans* whereas the compounds **168a–g** were active against *Aspergillus flavus*. Compounds **170a–g** were found to exhibit good antibacterial activity against *E. coli* and *P. aeruginosa* in addition to a pronounced effect on the growth of fungi like *Rhodotorula rubra*, *C. albicans* and *Lipomyces lopofera* whereas compounds **172a–g** were active against *Staphylococcus aureus*, *Staphylococcus albus*, *E. coli* and *P. aeruginosa*.



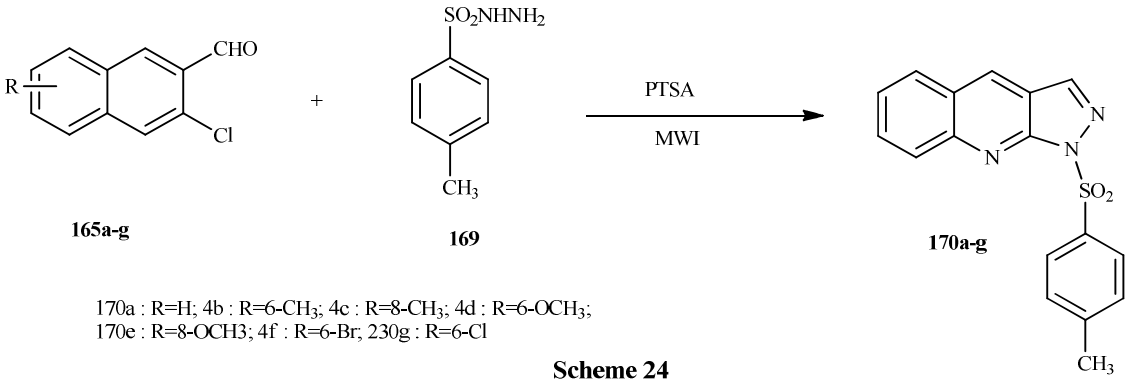
165a-g **166** **167a-g, 168a-g**

167 : X = O; 228: X = S

167a : R=H; 2b : R=7-CH_3; 2c : R=9-CH_3; 2d : R=7-OCH_3; 167e : R=9-OCH_3; 2f : R=7-Br; 227g : R=7-Cl

168a : R=H; 3b : R=7-CH_3; 3c : R=9-CH_3; 3d : R=7-OCH_3; 168e : R=9-OCH_3; 3f : R=7-Br; 228g : R=7-Cl

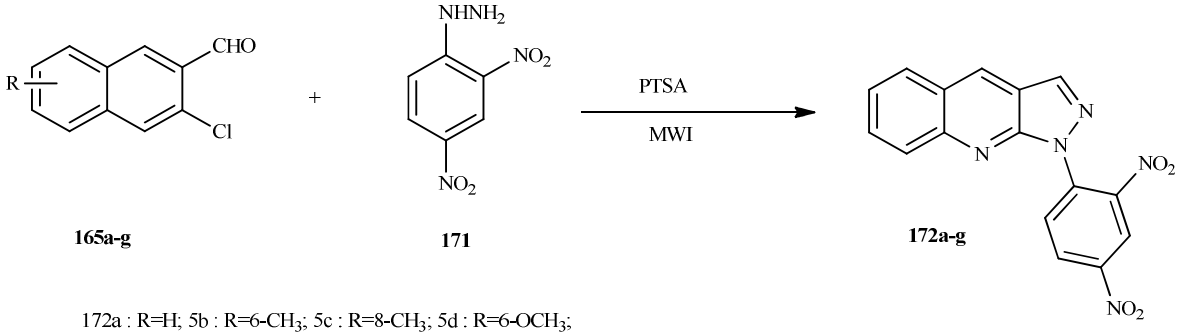
Scheme 23



165a-g 169 170a-g

170a : R=H; 4b : R=6-CH_3; 4c : R=8-CH_3; 4d : R=6-OCH_3;
170e : R=8-OCH3; 4f : R=6-Br; 230g : R=6-Cl

Scheme 24

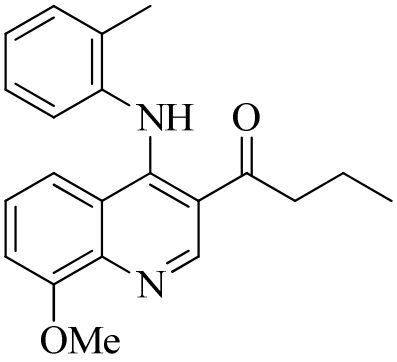


165a-g 171 172a-g

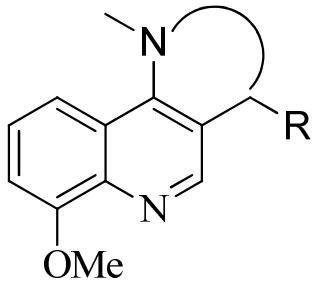
172a : R=H; 5b : R=6-CH_3; 5c : R=8-CH_3; 5d : R=6-OCH_3;
172e : R=8-OCH_3; 5f : R=6-Br; 5g : R=6-Cl

Scheme 25

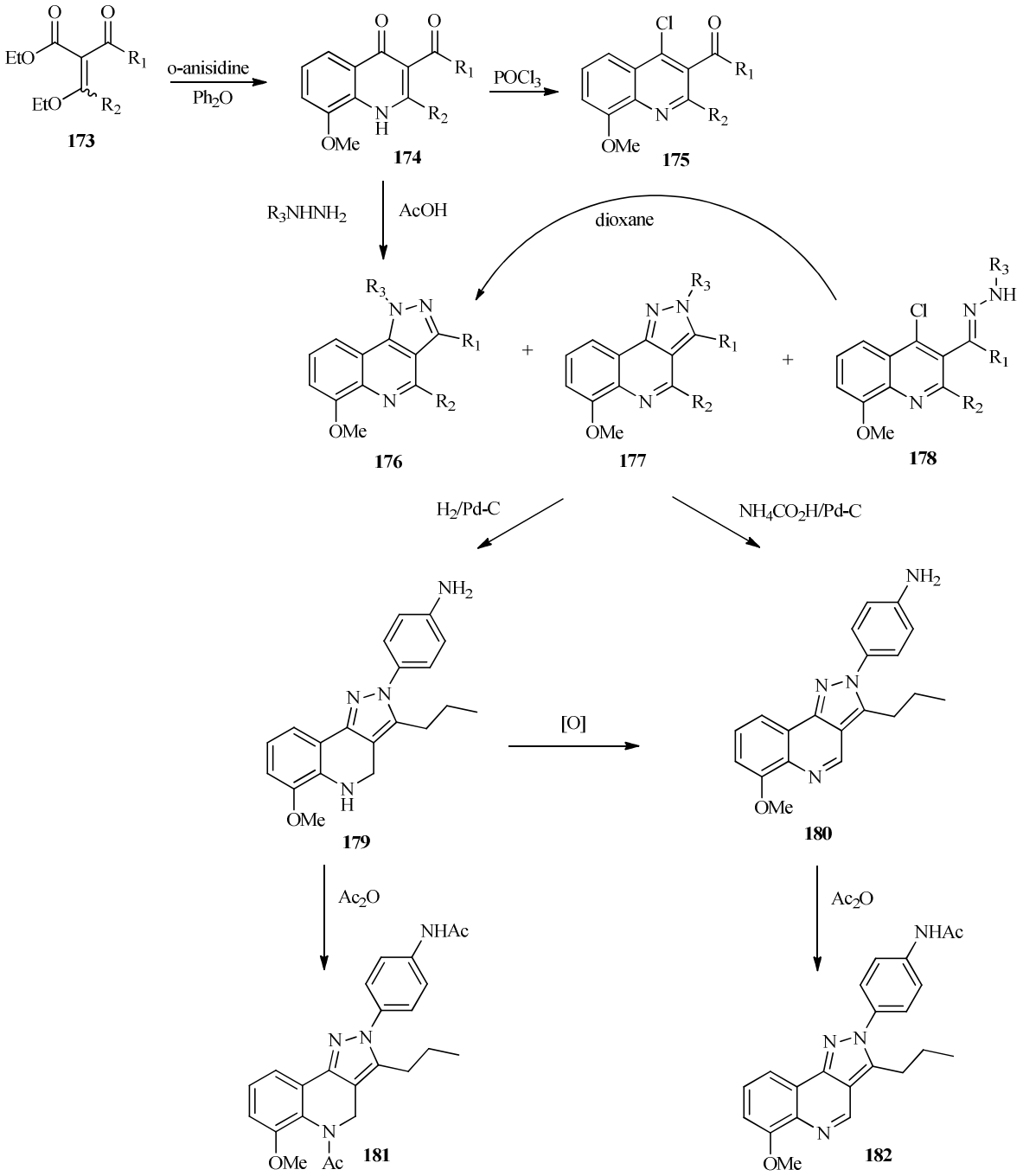
Kalayanov *et.al.,*[32] have synthesized a series of 1-aryl-1H-pyrazolo[4,3-c]quinolines and 2-aryl-2H-pyrazolo[4,3-c]quinolines (**Scheme 26**) and evaluated them for their H^+/K^+- ATPase activity. They synthesized these molecules based on the reversible proton pump inhibitor, **SK and F 96067**.



SK and F 96067



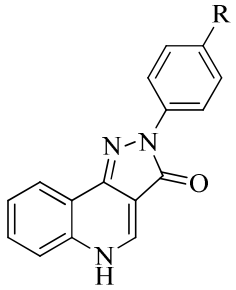
The carbonyl group present in the **SK and F 96067** was found to be responsible for the restriction of the NH group conformation by forming a hydrogen bond with the carbonyl and also by increasing the conjugation between the nitrogen and quinolines ring. 1H-Pyrazolo[4,3-c]quinolines were, therefore. synthesized in order to reduce the flexibility of the molecule. All the synthesized molecules were evaluated for their antiulcer activity using SK and F 97067 was used as the standard. The activity of the synthesized molecules was found to be lower than that of the standard.



Scheme 26

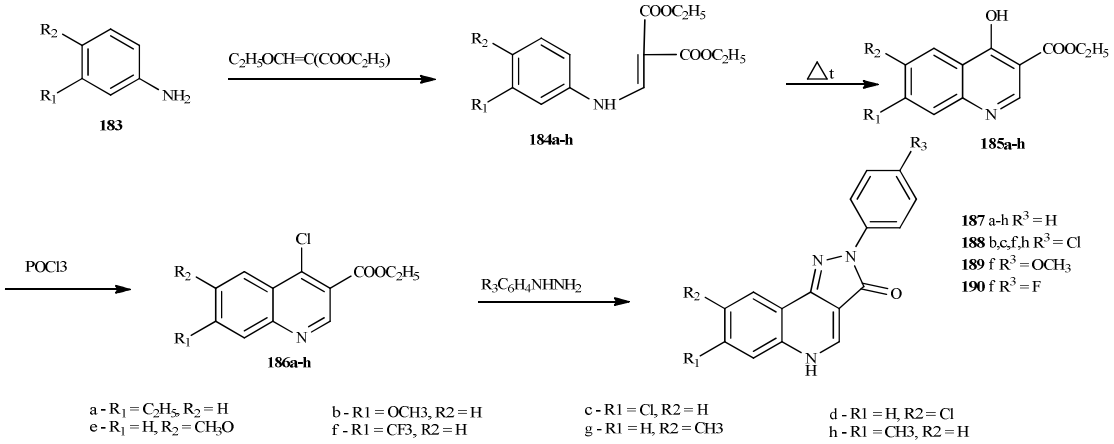
Wojciechowska *et al.*[33] have reported some pyrazoloquinolines having affinity for benzodiazepine receptors. They synthesized pyrazoloquinoline based on the scaffold pyrazolo[4,3-c]quinolin-3-ones, known for their affinity for benzodiazepine receptors. Studies were carried out to explain the effect of different substituents in pyrazolo[4,3-c]quinolin-3-ones. A series of 6- and 7-substituted-2-arylpyrazolo[4,3-*c*]quinolin-3-ones were synthesized (**Scheme 27**) and evaluated for their benzodiazepine receptor binding in competition with flunitrazepam. The target molecules were synthesized from diethyl ethoxymethylenemalonate *via* condensation with a suitable aniline. The product was further treated with $POCl_3$ and phenylhydrazine to obtain the final

compounds. The partition coefficient and electronic parameters used in correlation regression were compared with the experimental data obtained. The results of the QSAR studies revealed that the hydrophobicity and the position of the bicyclic core are both important for the binding affinity for the benzodiazepine receptor. The authors also successfully evaluated the structure-activity relationship of pyrazoloquinolines and explained the effect of the substituents on the pyrazoloquinoline scaffold.



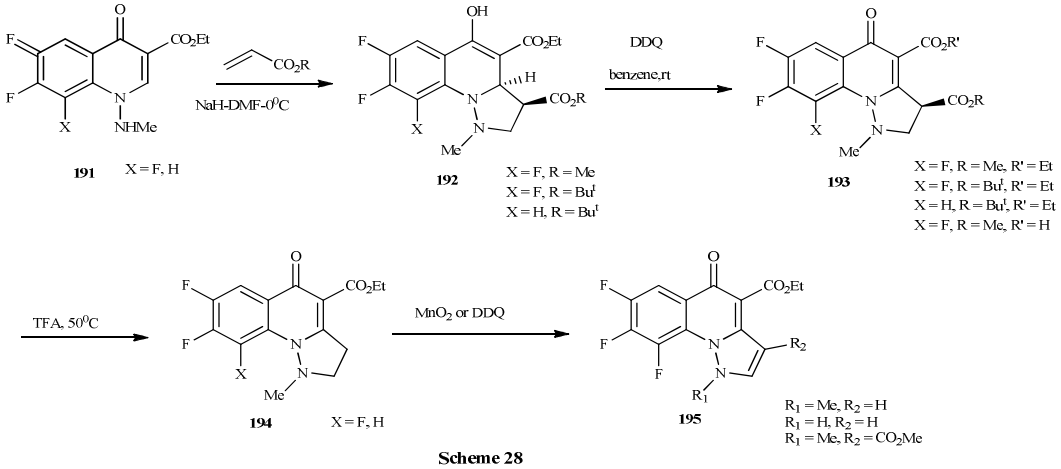
CGS 8216 R = H
CGS 9895 R = OCH_3
CGS 9896 R = Cl

pyrazolo[4,3-c]quinolin-3-ones

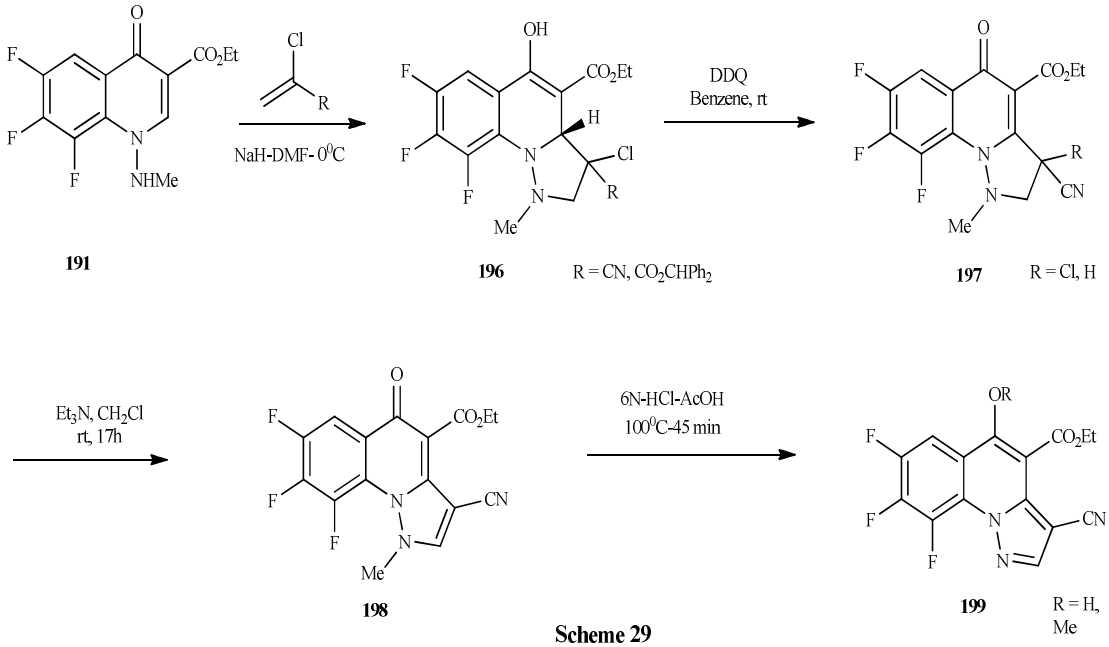


Scheme 27

David Barrett *et al*.[34] have reported a novel synthesis of pyrazolo[1,5-*a*] quinolines in excellent yields *via* a tandem Michael reaction of *N*-methylaminoquinolones with various acrylate derivatives in the presence of NaH (**Scheme 28**). The synthesized compounds were converted to DNA gyrase inhibitors by reaction with secondary amines (**Scheme 29**). The *in vitro* antibacterial studies carried out on the synthesized molecules, however, revealed that these derivatives were weak when compared to the standard, levofloxacin.

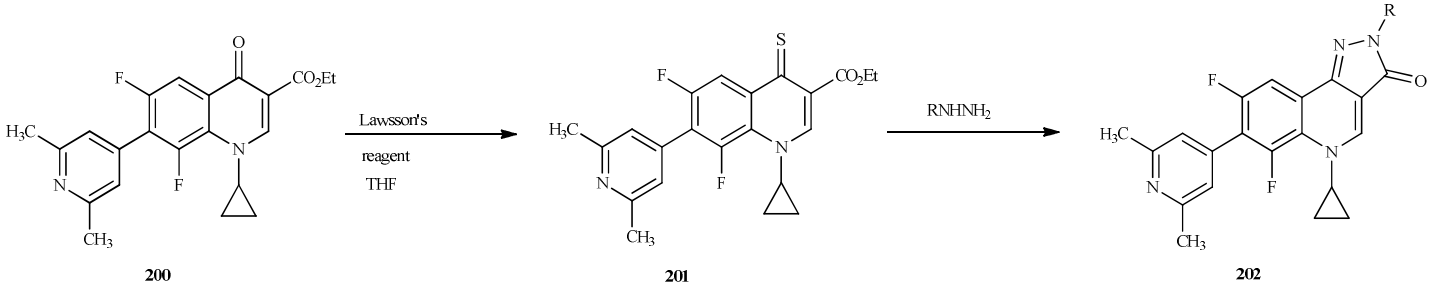


Scheme 28



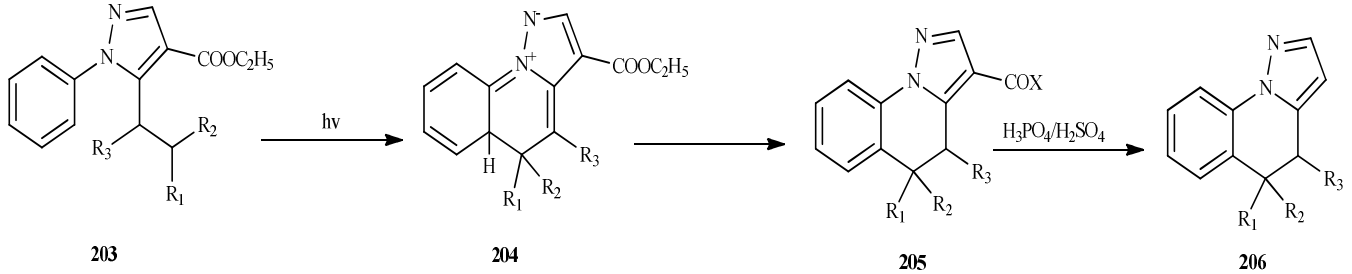
Scheme 29

Wentland *et al*.,[50] have studied the topoisomerase II inhibitory activity of a quinolone derivative and related compounds (**Scheme 30**). They demonstrated that significant enhancement in topoisomerase II inhibition on introducing a keto group and carboxylate group in the pyrazole ring.



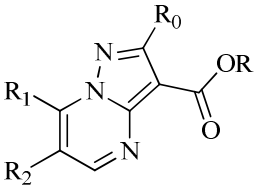
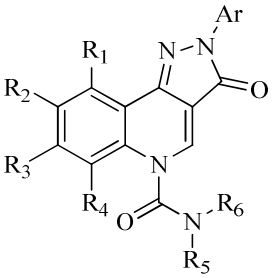
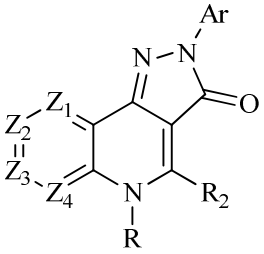
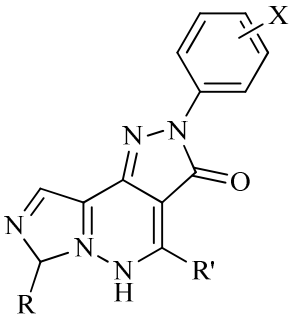
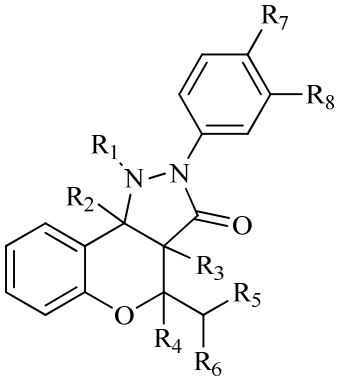
Scheme 30

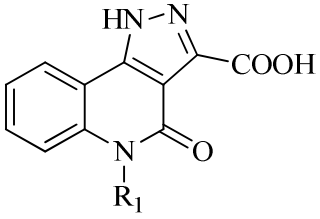
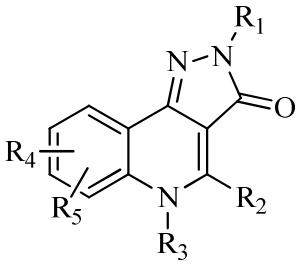
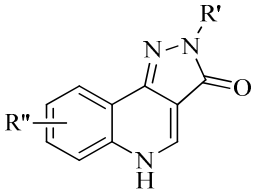
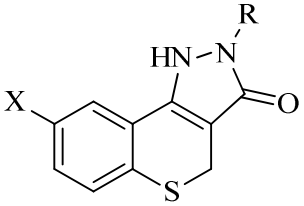
One of the earliest reports on the synthesis of 4,5-dihydropyrazolo[1,5-*a*]quinolines was by Deshayes *et al*., [35]. They explored the photo reactivity of a series of 5-alkenyl or dialkenyl-1-phenylpyrazoles and carried out the reaction under N_2 atmosphere using benzene as the solvent (**Scheme 31**). They did not, however, carry out the biological evaluation of these molecules

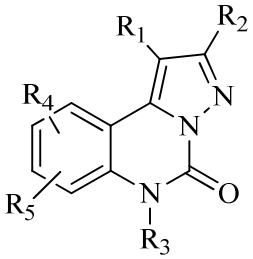


Scheme 31

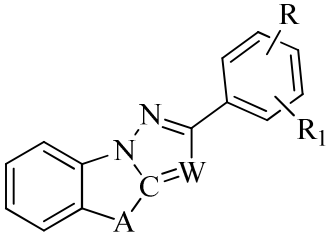
Some of the patents related to pyrazoloquinolines are summarized below,

Patent number	Biological activity	Compound
EP 2 520 577 A1 Nov 7, 2012	Central cannabinoid receptor (CB1) antagonizing activity.	
US 7 863 266 B2 Jan 4 2011	GABA receptor modulator	Pyrazolo[4,3-c]quinolin-3-one 
US 7 858 614 B2 Dec 28, 2010	GABA receptor modulator	Pyrazolo[4,3-c]quinolin-3-one 
US 7 081 456 B2 July 25, 2006	Immunomodulation, Rheumatoid arthritis, multiple sclerosis, diabetes, asthma, psoriasis.	
US 6 642 249 B2 Nov 4, 2003	Immunomodulation, Rheumatoid arthritis, multiple sclerosis, diabetes, asthma, psoriasis.	

US 5 442 065 Aug 15, 1995	Antiinflammatory agents	1H-pyrazolo[4,3-c]quinol-4(5H)-one-carboxylicacid 
US 4 560 689 Dec 24, 1985	Benzodiazepine receptor modulators	Pyrazolo[4,3-c]quinolin-3-one  R1 = quinolyl, isoquinolyl,pyrimidyl, thiazolyl R2 = R3 = H, alkyl R4 = H, alkyl, alkoxy, halogen, CF3
US 4 312 870 Jan 26 1982	Psychoactive drug for treatment of anxiety and depression.	2-arylpyrazolo[4,3-c]quinolin-3-one  R' = Ph, R" = Ph, Pyridyl, alkylpyridyl, halopyridyl R" = H, alkyl,alkoxy, alkylthio, OH, halo, CF3, nitro, amino, mono- or dialkylamino, CN, carbamoyl, or carboxy
US 4 268 516 May 19, 1981	Immuno regulators.	Benzothiopyrano[4,3-c]pyrazoles 
US 4 076 818 Feb 28, 1978	Bronchodialators, antihistamine,Antiinflammatory agent and for rheumatois arthritis.	Pyrazolo[1,5-c]quinazoline



US 4 024 149 May 17, 1977	Antifertility drug	Triazolo[1,5-a]quinolines



CONCLUSIONS AND FUTURE PERSPECTIVES

In conclusion, sydnones are versatile and privileged structures which belong to the mesoionic class of compounds. They possess a wide variety of biological activities and undergo a large number of reactions like cycloaddition, alkylation, arylation, lithiation, etc. Cycloaddition reactions have been one of the most exploited reactions of sydnones. This has been a stepping stone for the discovery of lead molecules. Among these, the reaction of sydnones to form pyrazoles are of considerable importance. The synthesis of pyrazoloquinolines have lead to the discovery of many biologically active molecules. Many pyrazoloquinolines have been evaluated for their anticancer, anticonvulsant, antibacterial and antifungal activities among others. Although sydnones and pyrazoloquinolines have been studied, fused ring derivatives of these molecules have been reported only sparingly. In Particular, sydnoquinolines and 4,5-dihydropyrazoloquinolines are yet to be explored, synthetically as well as biologically.

Pyrazoloquinolines are known for their ability to bind with Adenosine receptor, benzodiazepine receptor, Chk1kinase, phosphodiesterase, ras and topoisomerase II. Although sydnones and pyrazoloquinolines have been widely studied, reports on 4,5-dihydrosydnoquinolines and 4,5-dihydropyrazolo[1,5-a]quinolines are sparingly found in literature. There is good scope to study these molecules adopting new synthetic strategies. The authors of this review have taken up the challenge to explore the synthetic routes for 4,5-dihydrosydnoquinolines and 4,5-dihydropyrazoloquinolines. The structural features of these molecules and their capability to bind with receptors have increased our interest in them. Presently work is in progress in our laboratories to synthesize and evaluate these molecules for their biological activity.

REFERENCES

[1] Ollis, W.D.; Ramsden, C. A. Mesoionic compounds. Adv Heterocycl Chem., 1976, 19,

[2] Kier,L.B.; Roche, E. B. Medicinal chemistry of the Mesoionic compounds. J Pharm Sci., 1967, 56, 149.

[3] Ackermann, E. On the pharmacology of sydnone and sydnonimine:A survey. Pharmazie, 1967, 22, 537.

[4] Pandey, V. K; Mukesh; Tandon, M. Synthesis and antiviral activity of quinazolinyl syndnones. Indian J Heterocycl Chem., 2006, 15, 399.

[5] Kalluraya, B.; Rahiman, M.A.; Banji, D. Sydnone derivatives: part V – synthesis and pharmacological properties of some novel triazolothiadiazepin. Indian J Chem., 2002, 41B, 1712.

[6] Dunkley, C. S.; Thoman, C. J. Synthesis and biological evaluation of a novel phenyl substituted sydnone series as potential antitumor agents. Bioorg Med Chem Lett., 2003, 13, 2899.
[7] Mallur, S. G.; Tiwari, A. K.; Chinna Raju, B.; Suresh Babu, K.; Zehra Ali, A.; Sastry, B. S.; Madhusudana Rao, J. Synthesis and evaluation of phenyl substituted sydnones as potential DPPH scavengers. Indian J Chem., 2007, 46B, 1686.
[8] Satyanarayana, K.; Deshpande, S. R.; Subbarao, B.; Rao, M .N. A.Synthesis and nitric oxide donor activity of phenylsydnones. Indian Drugs, 2002, 39, 578.
[9] Tandon, V.K.; Yadav, D.B.; Chaturvedi, A.K. and Shukla, P.K. Synthesis of (1,4)-naphthoquinono-[3,2-c]-1H-pyrazoles and their (1,4)-naphthohydroquinone derivatives as antifungal, antibacterial, and anticancer agents, 2005, 15(1), 3288-3291.
[10] El-Deeb, I.M. and Lee,S.H. Design and synthesis of new potent anticancer pyrazoles with high FLT3 kinase inhibitory selectivity. 2010,18(11), 3961–3973.
[11] Godaginamath,G.S.; Pujar,S.R.; Kavali,R.R., Chemoselective reaction of 1-p-acetanilido-3-acetyl-5-hydroxy-2-methylindole towards methyl chloroacetate: Synthesis and anti-inflammatory activity of some new 5-pyrrolyl/oxadiazolyl/triazolyl/quinazolinylmeth o-xyindole derivatives. Indian J. Chem. 2003, 42[B], 2023.
[12] Salgin-Goksen U.; Gokhan-Kelekci N.; Goktas O.; Koysal Y.; Kihc E.; Isik S; Aktay G.;Ozalp, M.. 1-Acylthiosemicarbazides, 1,2,4-Triazoles-5(4H)-thiones, 1,3,4-Thiadiazoles and Hydrazone Containing 5-Methyl-2-benzoxazolinones: Synthesis, analgesic, anti-inflammatory and antimicrobial activities,Bioorg. Med. Chem. 2007, 15(17), 5738-5751.
[13] Onkol T., Sahin M.F., Yildirim E., Erol K., Ito S. Synthesis and antinociceptive activity of (5-chloro-2(3H)-benzoxazolon-3-yl)propanamide derivatives. Arch. Pharm Res. 2004, 27, 1068-1092.
[14] Wentland, M. P.; Suzanne C. Aldous, Monte D. Gruett, Robert B. Perni, Ronald G. Powles, Deborah W. Danz, Kristina M. Klingbeil, A.Danielle Peverly, Ronald G. Robinson, Thomas H. Corbett, James B. Rake, Susan A. Coughlin. The antitumor activity of novel pyrazoloquinoline derivatives. Bioorganic & Medicinal Chemistry Letters, 1995, 5(4), 405-410.
[15] Yang, S.W.; Smotryski, J.; McElroy, W. T.; Tan, Z.; Ho, G.; Tulshian, D.; William J. Greenlee, Guzzi, M.; Zhang, X.; Mullins, D.; Xiao, L.; Hruza, A.; Chan,M.T.; Rindgen, D.; Bleickardt, C. and Hodgson, R. Discovery of orally active pyrazoloquinolines as potent PDE10 inhibitors for the management of schizophrenia. Bioorganic & Medicinal Chemistry Letters. 2012, 22, 235–239.
[16] Faidallah, H.M. and Rostom, S.A.F. Synthesis, in vitro antitumor evaluation and DNA-binding study of novel tetrahydroquinolines and some derived tricyclic and tetracyclic ring systems. European Journal of Medicinal Chemistry, 2013, 63, 133-143.
[17] Kato,J.Y.; Aoyama, H. and Yokomatsu, T. Development of a new cascade reaction for convergent synthesis of pyrazolo[1,5-a]quinoline derivatives under transition-metal-free conditions. Org. Biomol. Chem., 2013, 11, 1171-1178.
[18] Mishra, A.P. 2D-QSAR study of 2, 5-dihydropyrazolo [4, 3-c] quinoline-3-one a novel series of PDE-4 inhibitors. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2012, 3 (1), 105-109.
[19] Chang, E.C.; Wen, Y.L.; Chang, C.H.; Shen, Y.H.; Wen, S.B.; Yeh, M.Y.; Wong, F.F. A novel one-pot synthesis of 2-arylpyrazoloquinolinone derivatives. Tetrahedron. 2012, 68, 5920-5924.
[20] Abu-Hashem, A.A. and Aly, A.S. Synthesis of new pyrazole, triazole and thiazolidine-pyrimido[4,5-b]quinolines derivatives with potential antitumor activity. Arch Pharm Res, 2012, 35(3), 437-445.
[21] Reis, R.R.; Azecedo, E.C.; de Souza, M.C.B.V. Ferreira,V.F.; Montenegro, R.C.; Araujo, A.J.; Pessoa, C.; Costa-Lotufo, L.V.; De Moraes, M.O.; Filho, J.D.B.M.;. De Souza, A.M.T.; De Carvalho, N.C.; Castro, H.C.;

Rodrigues, C.R. and Vasconcelos, T.R.A. Synthesis and anticancer activities of some novel 2-(benzo[d]thiazol-2-yl)-8-substituted-2H-pyrazolo[4,3-c]quinolin-3(5H)-ones. European Journal of Medicinal Chemistry, 2011, 46, 1448-1452.

[22] Lenzi, O.; Colotta, V.; Catarzi, D.; Varano, F.; Squarcialupi, L.; Filacchioni, G.; Varani, K.; Vincenzi, F.; Borea, P. A.; Ben, D.D.; Lambertucci, C.; Cristalli, G. Synthesis, structure–affinity relationships, and molecular modeling studies of novel pyrazolo[3,4-c]quinoline derivatives as adenosine receptor antagonists Bioorganic & Medicinal Chemistry. 2011, 19, 3757–3768.

[23] Imbriglio, J.E.; DiRocco, D.; Bodner, R.; Raghavan, S.; Chen, W.; Marley, D.; Esser, C.; Holt, T.G.; Wolff, M.S.; Taggart, A.K.P.; Waters, M.G.; Tata, J.R. and Colletti, S.L. The discovery of high affinity agonists of GPR109a with reduced serum shift and improved ADME properties. Bioorganic & Medicinal Chemistry Letters, 2011, 21, 2721–2724.

[24] Hang, C.; Li, Q.; Zhu, Y. and Katayama, H. Copper(I)-Catalyzed Tandem Cyclization/Condensation Reaction to Novel 4,5-Dihydropyrazolo[1,5-a]quinolines and Pyrazolo[1,5-a]indoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 2011, 41(22), 3318-3324.

[25] Colotta, V.; Capelli, F.; Lenzi, O.; Catarzi, D.; Varano, F.; Poli, D.; Vincenzi, F.; Varani, K.; Borea, P.A.; Ben, D.D.; Volpini, R.; Cristalli, G. and Filacchioni, G. Novel potent and highly selective human A3 adenosine receptor antagonists belonging to the 4-amido-2-arylpyrazolo[3,4-c]quinoline series: Molecular docking analysis and pharmacological studies. Bioorganic & Medicinal Chemistry, 2009, 17, 401–410.

[26] Duggineni, S.; Sawant, D.; Saha, B. and Kundu, B. Application of modified Pictet–Spengler reaction for the synthesis of thiazolo- and pyrazolo-quinolines. Tetrahedron. 2006, 62, 3228–3241.

[27] Selvi, T.S.; Nadaraj, V.; Mohan, S.; Sasia, R. and Hema, M. Solvent free microwave synthesis and evaluation of antimicrobial activity of pyrimido[4,5-b]- and pyrazolo[3,4-b]quinolines, Bioorganic & Medicinal Chemistry, 2006, 14 ,3896–3903.

[28] Kalayanov, G.D.; Kang, S.K.; Cheon, H.G.; Lee, S.G.; Yum, E.K.; Kim, S.S. and Choi, J.K. Synthesis of Pyrazoloquinolines as Gastric H+/K+-ATPase Inhibitors, Bull. Korean Chem. Soc.1998, 19(6), 667-671.

[29] Wojciechowska, J.K.; Lange, J.; Ksiazek, W.; Gniewosz, M. and Rump, S. Structure-activity relationship investigations of the modulating effect of core substituents on the affinity of pyrazoloquinolinone congeners for the benzodiazepine receptor. Il Farmaco, 1998, 53, 579-585.

[30] Barrett, D.; Sasaki, H.; Kinoshita, T.; Fujikawa, A. and Sakane, K. A novel synthesis of Pyrazolo[1,5-a]quinolines ring system. New N1-C2 bridged DNA gyrase inhibitors via a novel tandem 1,4-conjugate addition-michael [3+2] annulation process. Tetrahedron, 1996, 52(25), 8471-8488.

[31] Wentland, M.P.; Aldous, S.C.; Gruett, M.D.; Perni, R.B.; Powles, R.G.; Danz, D.W.; Klingbeil, K.M.; Peverly, A.D.; Robinson, R.G.; Corbctt, T.H.; Rake, J.B. and. Coughlin, S.A. The antitumor activity of novel pyrazoloquinoline derivatives. Bioorganic and Medicinal Chemistry Letters. 1995, 5(4), 405-410.

[32] Deshayes, C. and Gelin, S. Photocyclization of 5-(1-alkenyl)-1-phenylpyrazoles: A convenient synthesis of 4,5-dihydropyrazolo[1,5-a]quinolines. Tetrahedron Letters, 1983, 24(43), 4679-4682.

[33] Tanimoto, K.O.; Oi, M.O.; Tsuboi, Y.O. and Moritani, Y.O. Pyrazolo[1,5-a]pyrimidine compounds as CB1 receptor antagonists. EP Patent 2 520 577 A1, November 7, 2012.

[34] Winters, G.; Odaso, G.; Galliani, G. and Lerner, L.J. 2-Phenylpyrazolo[1,5-a]quinolines compounds. US Patent 4 024 149, May 17, 1977.

[35] Magnus, P.D.; Iliadis, T.;Eisenbeis, S.A. and Fairhurst, R.A. Synthesis of tetrahydroquinoline enediyne core analogues of dynemicin. US Patent 5 442 065,Aug 15, 1995.
[36] Vogt, B.R. Pyrazolo[1,5-c]quinazoline derivatives and related compounds. US Patent 4 076 818, Feb 28, 1978.
[37] Lambordino, J.G.; Otterness, I.G. and Muren, J.F. Benzothiopyrano[4,3-c]pyraozoles as immunoregulatory agents. US Patent 4 268 516, May 19, 1981.
[38] Yokoyama, N. Pyrazoloquinolines. US Patent 4 312 870, Jan 26 1982.
[39] Yokoyama, N. Heterocyclic fused pyrazolo[3,4-d]pyrdin-3-ones as benzodiazepine receptor modulators. US Patent 4 560 689, December 24, 1985.
[40] Kaplan, P.A. and Gupta, V. Therapeutic pyrazoloquinoline urea derivatives. US Patent 7 863 266 B2, Jan 4 2011.
[41] Kaplan, A.P.; Gupta, V.; Wasley, J.W.F. Therapeutic pyrazolonaphthyridine derivatives. US Patent 7 858 614 B2, Dec 28, 2010.
[42] Matthews, I.A.; Coulter, T.S.; Ghiron, C.; Brennan, C.J.; Kamal Uddin, M.; Pettersson, L.O.G.; Thrige, D.G.; Huxley, P. .Immunomodulatory compoundsUS Patent 7 081 456 B2, July 25, 2006.
[43] Bjork, P.A.; Fex, T.;Pettersson, G.;Soreson. P.;Thrige, D.G. Immunomodulating compounds. US Patent 6 642 249 B2, Nov 4, 2003

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