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Review article

Pyrazoloquinazolines: Synthetic strategies and bioactivities



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ABSTRACT

Numerous *N*-heterocycles are indisputably evidenced to exhibit myriad biological activities. In the recent past, attempts made to condense the various heterocycles have resulted in derivatives possessing better bioactivities. Among many such condensed heterocycles, pyrazoloquinazolines have managed to hold the attention of many researchers, owing to the broad spectrum of activities they portray. This review is the first of its kind to congregate the various pyrazoloquinazolines reported until now and categorizes these structurally isomeric classes into eleven different groups based on the fusion pattern of the ring such as [1,5-c], [5,1-b], [4,3-h], etc. Furthermore, this review is a concerted effort to highlight design, synthetic strategies as well as biological activities of each class of this condensed heterocycle. Structure-activity relationship studies and *in silico* approaches wherever reported have also been discussed. In addition, manuscript also offers scope for design, synthesis and generation of libraries of unreported classes of pyrazoloquinazolines for the biological evaluation.

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1. Introduction

Numerous *N*-heterocyclic [1] compounds exhibiting broad spectrum of diverse bioactivity are reported and also found to be successfully implicated in industries ranging from pharmaceuticals to agrochemical based. At present, massive number of heterocycles [2] are being explored, which have resulted from various combinations of the basic scaffolds like imidazole [3], thiazole [4], piperidine [5], pyridine [6], pyrrole [7], pyrrolidine [8], indole [9], purine [10], quinoline [11], isoquinoline [12] etc. Among the many heterocycles, pyrazoles [13] have shown promising biological activity in various human ailments. Celecoxib [14], fipronil [15], lonazolac [16], zaleplon [17], allopurinol [18], indiplon [19] and viagra [20] are some of the drugs containing pyrazolo [21] moiety and exhibiting potent biological activities ranging from anti-inflammatory to phosphodiesterase inhibitory activity [22]. Since last two decades quinazolines [23] and its derivatives have gained significant attention leading to emergence of some popular drugs such as erlotinib, an anticancer [24], prazosin, an adrenergic

blocker [25], and iressa [26], an epidermal growth factor receptor inhibitor. Literature confirms the significant enhancement in selectivity and potential of the bioactivity as a result of pyrazole fusion with other heterocycles e.g. pyrazolopyrimidines [27,28], indazole [29], pyrazolopyridines [30], pyrazolopiperidines [31] etc. Pyrazole fused with quinazoline [32] might escalate the selectivity and sensitivity of the fused heterocycle against life-altering diseases. The most recent report by Li et al. compiles only the synthetic methods for condensed pyrazole derivatives, briefly covering pyrazolo[1,5-c]quinazolines, pyrazolo[4,3-h]quinazolines and pyrazolo[4,3-f]quinazolines [33] only. However, the present mini-review is the first of its kind to congregate the various pyrazoloquinazolines reported until now and to categorize the structurally isomeric classes into eleven different groups (Fig. 1 and Fig. 2) on the basis of their ring fusion such as [1,5-c], [5,1-b], [4,3-h], etc. Furthermore, this review is a concerted effort to highlight design, synthetic strategies as well as *in vitro* and *in vivo* biological activities, SAR of each class of this condensed heterocycles.

2. Classification

Pyrazoloquinazolines were categorized into eleven different groups depending on the site of ring fusion. Each class has been elaborated vividly in the subsequent sections.

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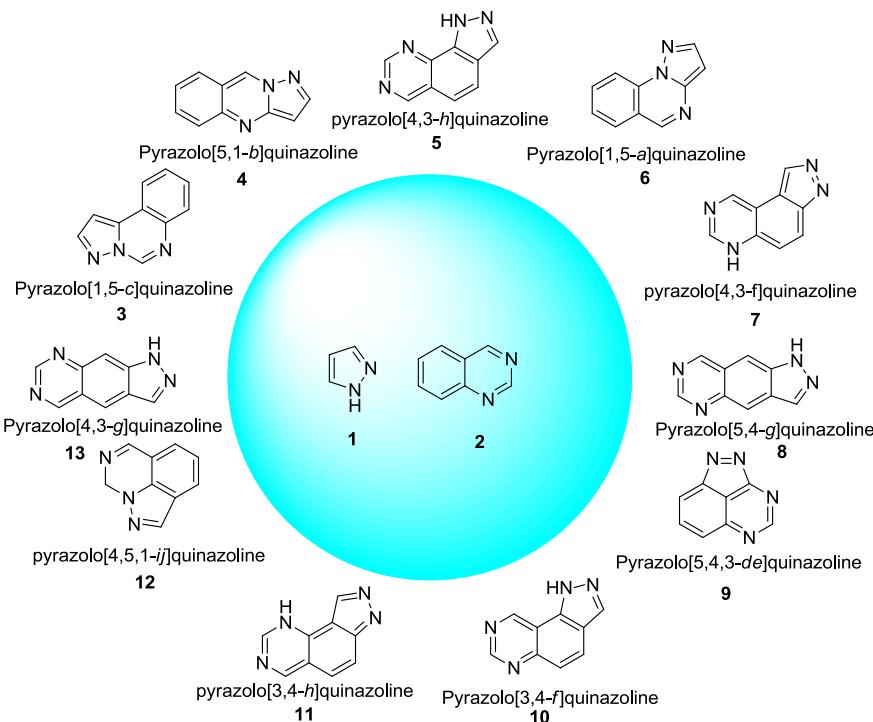


Fig. 1. Chemical structures of possible condensed pyrazoloquinazolines.

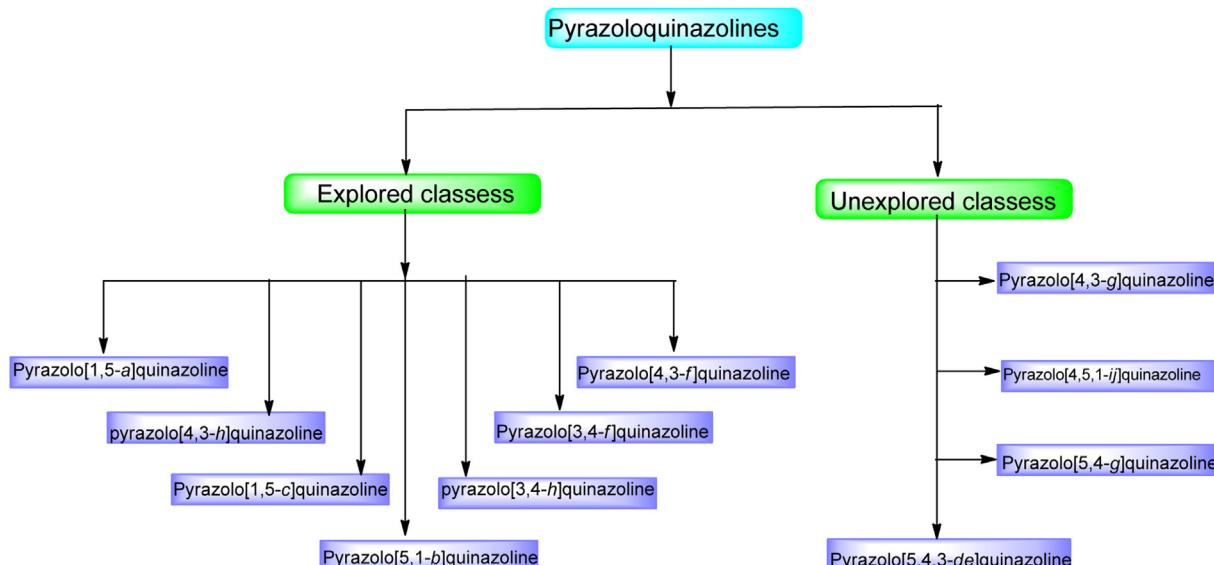


Fig. 2. Classes of pyrazoloquinazolines reported till date.

3. Pyrazolo[1,5-c]quinazolines

3.1. Synthetic strategies

Research and development in the field of pyrazoles has highlighted various strategies for the successful synthesis of pyrazolo[1,5-c]quinazolines, outlined in Fig. 3. In 2002, Alkhathal et al. carried out the reaction of hydrazones of 2-aminoacetophenone with triphosgene in dichloromethane or benzene in the presence of triethylamine (route-a) [34]. In 2002, Varano et al. catalytically reduced 2-nitroarylpyrazoles to give **14** (route-b) [35] and in 2005,

same research group established the synthesis of pyrazolo[1,5-c]quinazoline-1,2-dicarboxylates by reaction of 3-diazo-1,3-dihydro-indol-2-one derivatives with an excess of diethyl acetylenedicarboxylate (route-c) [36]. In 2012, Yang et al. synthesized pyrazolo[1,5-c]quinazolines by the treatment of 1-(2-halophenyl)-3-alkylprop-2-yn-1-ones with hydrazine hydrochloride in the presence of Cs_2CO_3 and DMSO in first step followed by addition of acetamidine hydrochloride under N_2 atmosphere (route-d) [22]. In 2013, Guo et al. demonstrated a copper-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with carbonyl compounds and aqueous ammonia under air (route-e) [37]. In 1996, Colotta et al.

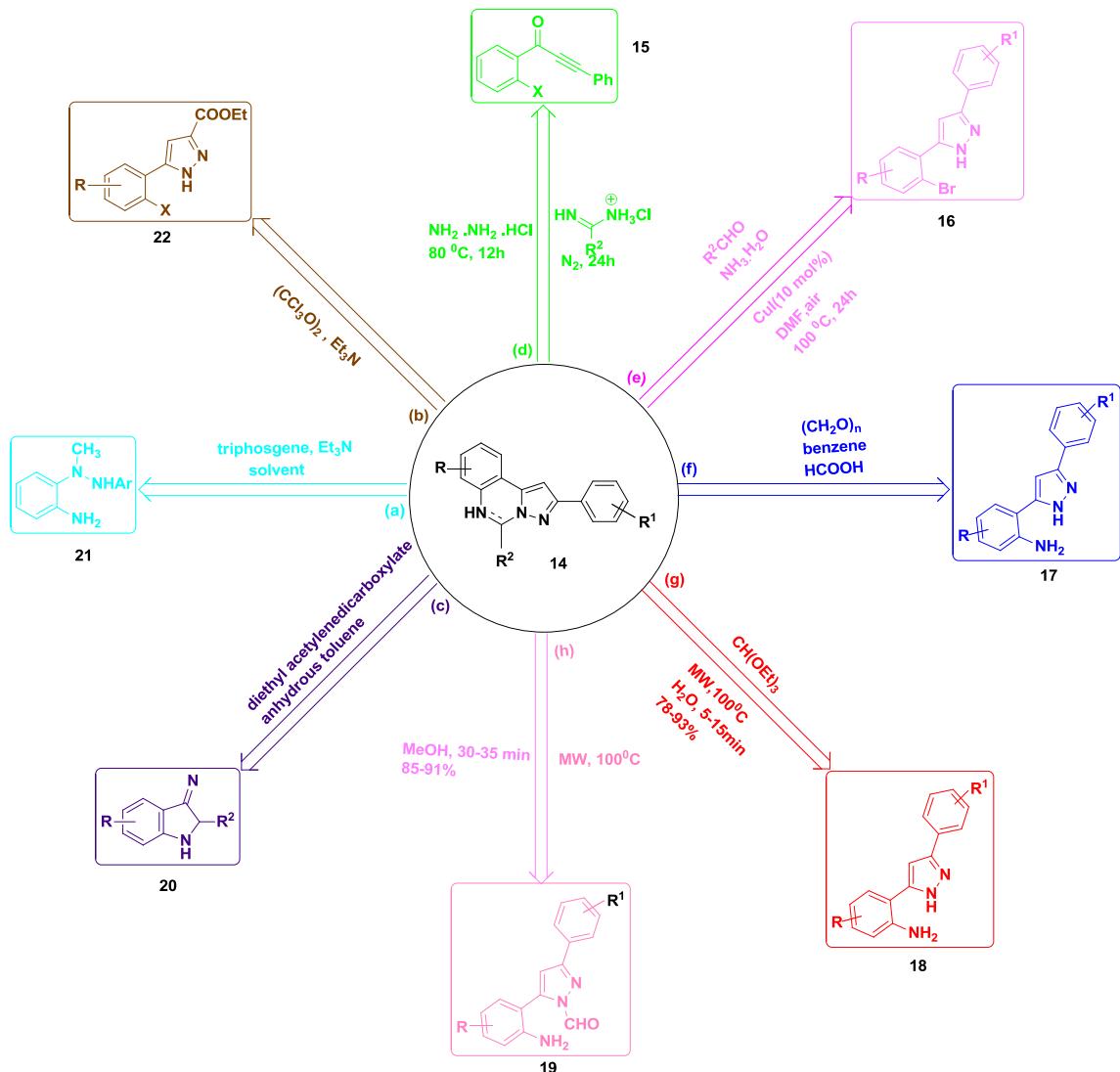


Fig. 3. Retro-synthetic routes for pyrazolo[1,5-c]quinazolines.

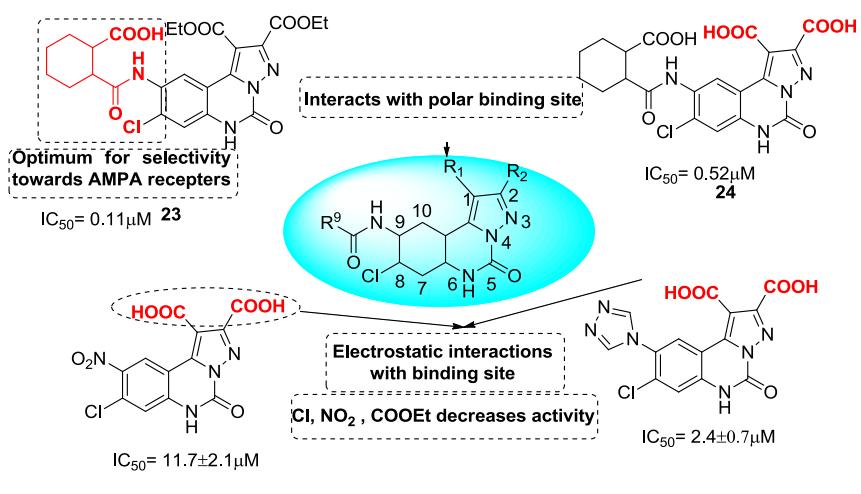
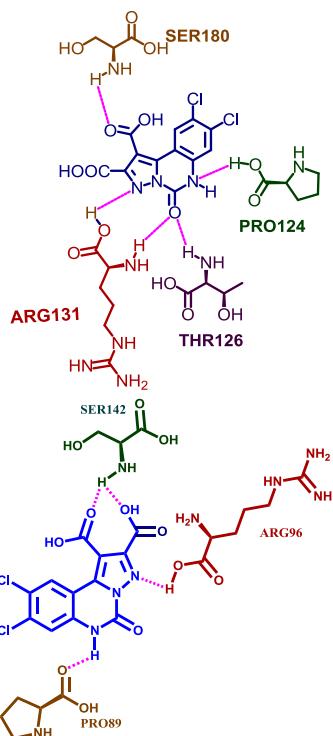


Fig. 4. SAR study of compounds 23–26 as Gly/NMDA and AMPA antagonist.



- Key points**
- AMPA receptor antagonists required Cl at position-8. 1,2-dicarboxylic acid. 2-carboxylbenzoyl amino substituent at position-9 for selectivity and activity.
 - The carboxylic acid interacts better due to electrostatic interactions to polar AMPA binding site

Fig. 5. Docking poses of 8,9-dichloro-5-oxo-5,6-dihydropyrazolo[1,5-c]quinazoline-1,2-dicarboxylic acid (**27**) with Gly/NMDA (left) and AMPA receptors (right).

refluxed 4,5-dihydro-3,5-diaryl pyrazoles with paraformaldehyde in benzene for 4–5 h (route-f) [38]. In 2014, our research group synthesized the target compounds by carrying out microwave-assisted cyclocondensation of 2-(3-aryl-1*H*-pyrazol-5-yl) anilines with various aldehydes/triethyl orthoformates (route-g) and internal cyclo-condensation of 5-(2-aminophenyl)-4,5-dihydro-3-arylpyrazole-1-carbaldehyde(route-h) [39].

3.2. Biological activities of pyrazolo[1,5-c]quinazolines

Pyrazolo[1,5-c]quinazolines have shown various biological activities such as AMPA, Gly/NMDA, KA antagonist, benzodiazepine receptor binding agonist, phosphodiesterase 10 A inhibitors, and anti-microbial and are discussed below.

3.2.1. AMPA, Gly/NMDA and KA receptor antagonists

Varano and his research group reported the AMPA (2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)-propionic acid) [40,41], Gly/NMDA (Glycine/N-methyl-D-aspartic acid) [42] and KA (kainic acid) [43] receptor binding affinity of 1,9-disubstituted-8-chloro-6a,7,8,9,10,10a-hexahydropyrazolo[1,5-c]quinazoline-5(6*H*)-one series and performed their docking studies. SAR studies (Fig. 4) established the presence of chlorine and a nitrogen containing heterocycle at position-8 and position-9, respectively, increase affinity towards AMPA receptor. The presence of 2-carboxylbenzoyl amino substituent at position-9 enhanced the Gly/NMDA and AMPA activity of compounds (**23** and **24**). Compound **23** showed maximum KA receptor selectivity as compared to Gly/NMDA receptors. The improved activity may be attributed to the presence of carboxyl groups at position-1 and 2 which due to its electrostatic interactions between negatively charged carboxylate group and positively charged site on receptors increased the affinity of **23**. Compound **25** showed highest affinity towards AMPA receptor whereas compound **26** exhibited highest affinity toward Gly/NMDA receptor. When carboxylic acid is present at position-1, AMPA receptor binding is maximum as it gets accommodated in the

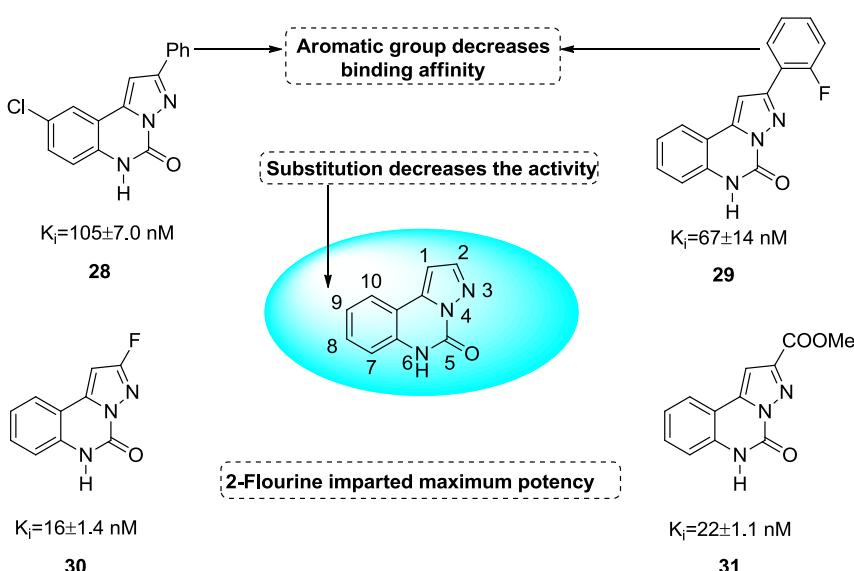


Fig. 6. SAR of **28–31** acting on benzodiazepine receptor.

- Key points**
- BZR activity decreases with the introduction of Cl atom at position-9.
 - BZR activity increases with the introduction of phenyl at position-2.
 - BZR activity increases with decreasing the size of ester group at position-2.

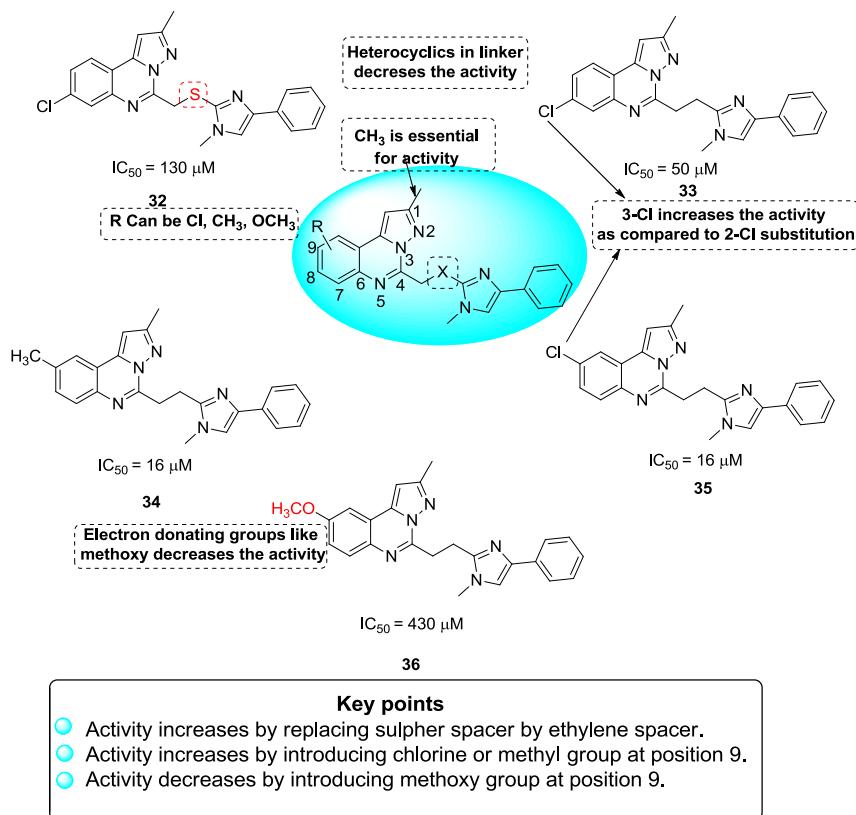


Fig. 7. SAR and IC₅₀ values of pyrazolo[1,5-c]quinazolinederivatives against phosphodiesterase 10A.

polar region as compared to the lipophilic groups (Cl, NO₂, COOEt). The replacement of 9-nitro group with heterocyclic moieties displayed more pronounced AMPA receptor binding affinity with respect to reference compound [44].

In 2005, the same research group carried out molecular modeling studies sing Glide and MOE (Molecular Operating Environment) on 1-Substituted pyrazolo[1,5-c]quinazolines to explore receptor affinity and selectivity of the synthesized new pyrazoloquinazoline derivatives as novel Gly/NMDA receptor antagonists. One of the derivatives, **27**, having effective binding at both the

receptors, showed interaction with the most important and highly conserved triad of residues crucial for binding the ligands on both receptors. Further it was observed that the interactions with arginine (Arg131 in the Gly/NMDA receptor and Arg96 in the AMPA receptor), threonine (Thr126 and Thr91, respectively), and proline residues (Pro124 and Pro89, respectively) were noteworthy with compounds (Fig. 5). Also, **27** showed an extra electrostatic interaction between the carboxylic moiety and the NH group of serine (Ser180 or Ser142) [36].

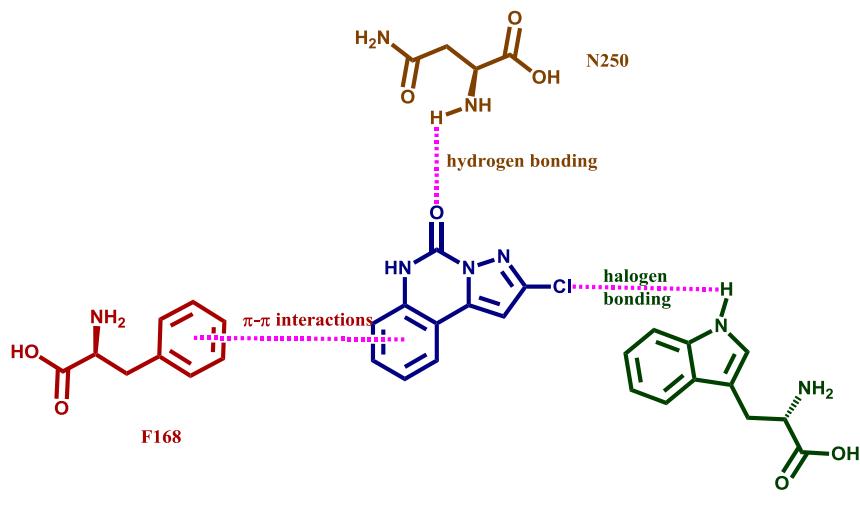


Fig. 8. Docking interaction of 2-chloropyrazolo[1,5-c]quinazlin-5(6H)-one (**37**)with adenosine receptor.

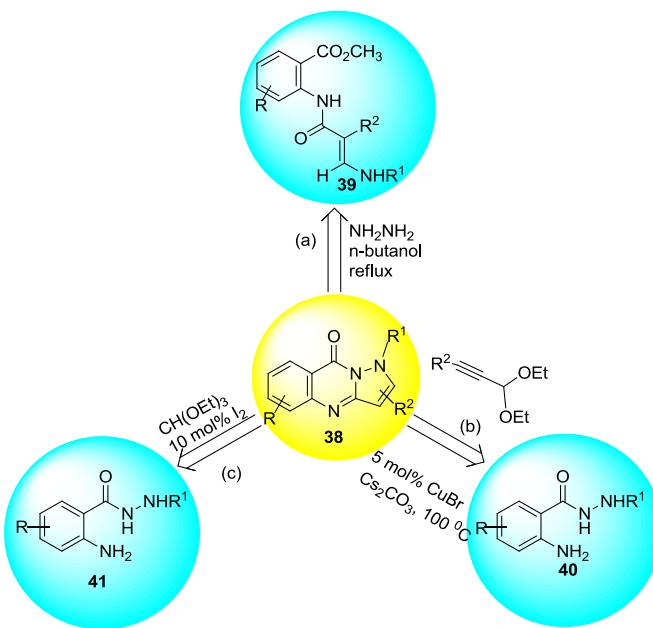


Fig. 9. Various retrosynthetic routes for pyrazolo[5,1-b]quinazolines.



Fig. 10. 7-(Benzylamino)-4,9-dihydro-4-methyl-9-oxo-pyrazolo[5,1-b]quinazoline-2-carboxylic acid (**42**).

3.2.2. Benzodiazepine receptor (BZR) binding affinity

Colotta et al. reported the binding affinity of pyrazolo[1,5-c]quinazoline-5-ones towards benzodiazepine receptors (BZR) [45–47]. They reported that the presence of a chlorine atom at position-9 and/or phenyl group at position-3 decreased the potency of the compounds against BZR (**28** and **29**). On the other

hand, introduction of a fluorine atom at *ortho*-position (**30**) increased the BZR binding activity (Fig. 6). It was also observed that the smaller size of ester group at position-2 escalated the binding activity (**31**) [38].

3.2.3. Phosphodiesterase 10A inhibitors

Asproni et al. characterized pyrazolo[1,5-c]quinazolines as a novel class of potent phosphodiesterase 10A (PDE10A) inhibitors and evaluated the compounds by yttrium tested silicate SPA beads assay [48–50]. The research group reported that CH₂ substitution at X increased the potency, which was decreased when replaced with sulfur. Electron withdrawing groups such as chlorine at position-9 afforded the most promising compounds (**33**, **34** and **35**) whereas the electron releasing groups like OCH₃ at position-9 brought about a decrease in the activity (**36**). Some of the important SARs are highlighted in the Fig. 7.

3.2.4. Adenosine receptor (AR) antagonist activity

In 2013, Catarzi et al., designed a number of 5-oxo-pyrazolo[1,5-i]quinazolines, bearing heteroaryl moiety at position-2 as hA₃ AR [51] antagonists [52–54]. Study produced some interesting compounds endowed with good hA₃ receptor affinity and high selectivity, being totally inactive at all the other AR subtypes. In contrast, the corresponding 5-amino derivatives do not bind or bind with very low affinity at the hA₃ AR. Evaluation of the synthetic intermediates led to the identification of some 5(3)-(2-aminophenyl)-3(5)-(heteroaryl)pyrazoles with high selectivity, but modest affinity, toward the hA₃ AR subtype [55]. Structure activity relationship studies revealed that replacement of the 2-phenyl group with suitable moieties significantly reinforced the receptor–ligand interaction, thus leading to enhanced hA₃ binding affinities. The 4-methoxy group improves the receptor–ligand interaction by forming a weak hydrogen bond with a suitable receptor site or by reinforcing the π–π stacking interaction of the 2-phenyl ring with the receptor, due to its electron-donating property. The lipophilic contribution of the methoxy group to the ligand interaction is negligible. In contrast, introduction of either the 4-methyl or the 4-chloro substituent strongly affects the hA₃ binding affinity probably by increasing the hydrophobic interactions at the level of the 2-phenyl substituent. Moreover, introduction at position-2 of the pyrazoloquinazoline scaffold of a 2-fluorophenyl,

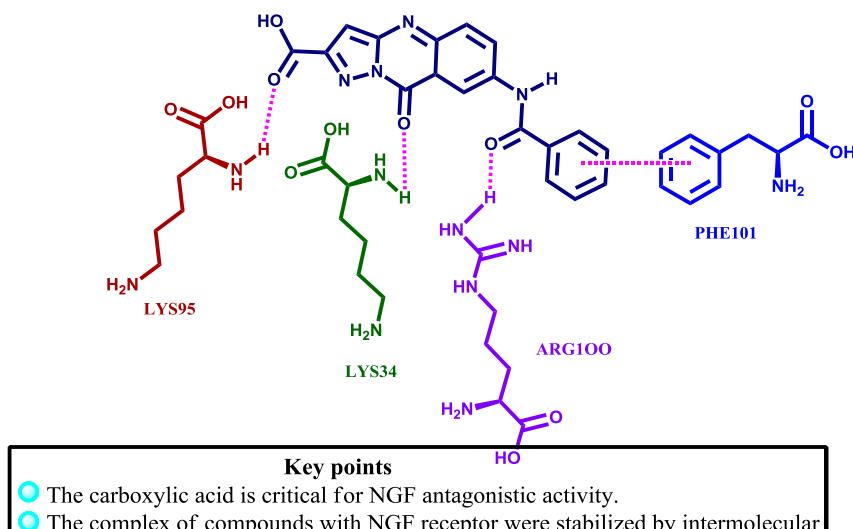
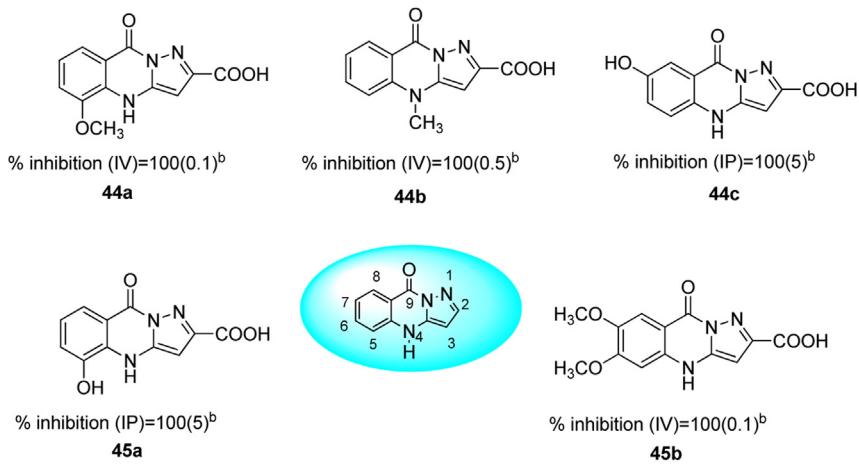


Fig. 11. Docking interactions of 7-benzamido-9-oxo-8a,9-dihydropyrazolo[5,1-b]quinazoline-2-carboxylic acid (**43**) with neurotropin nerve growth factor.



where b is significantly different from control($p<0.05$)

Key points

- Activity increases with the introduction of methyl group at position-4.
- Activity increases with the introduction of hydroxyl group at positions-5 and 7.
- Activity increases with the introduction of dimethoxy analogues.

Fig. 12. SAR and anti-allergic activity of pyrazolo[5,1-b]quinazoline derivatives.

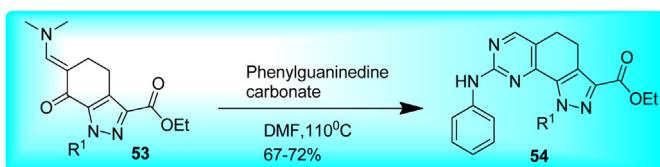
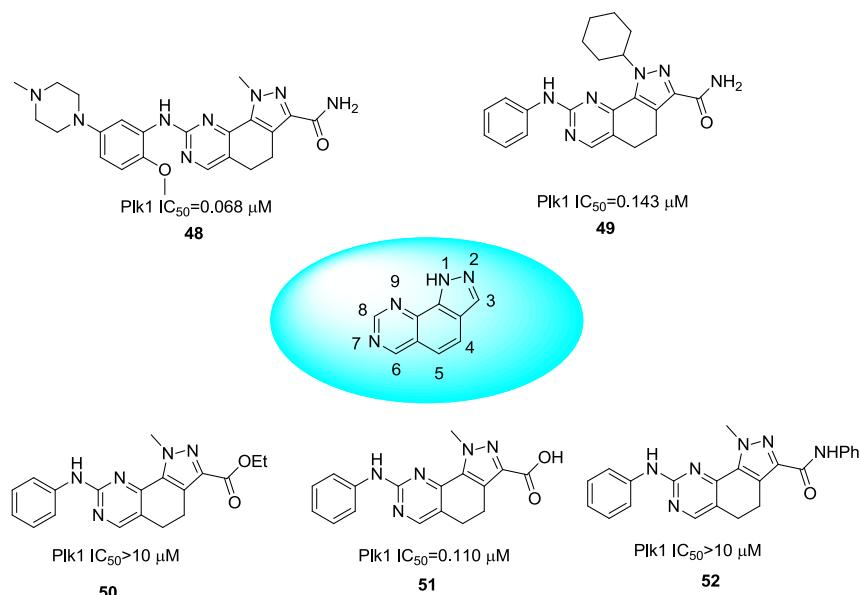


Fig. 13. Synthesis of pyrazolo[4,3-h]quinazoline.

2-furyl, 2-thienyl or 2-pyridil moiety improves the hA3 receptor–ligand interactions with respect to the parent compound. This has been due to the presence, of an heteroatom at the position-2, which is able to reinforce the binding with the receptor through a hydrogen bond [55].

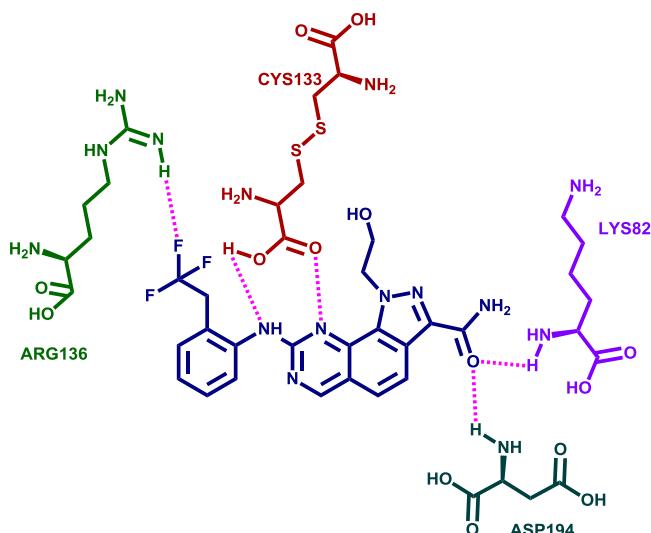
Compound 37 interacts with Val169 and Asn250 forming hydrogen bond (Fig. 8). The phenyl ring shows $\pi-\pi$ interaction with Phe118. The other major interactions observed and recorded were Phe168, Leu90, Trp94, Phe243 [55].



Key points

- Activity decreases by the introduction of bulky group at position-1.
- Activity decreases by the introduction of ester, carboxylic acid residue or secondary amide at position-3.

Fig. 14. IC_{50} values of Plk1 inhibitors.

**Key points**

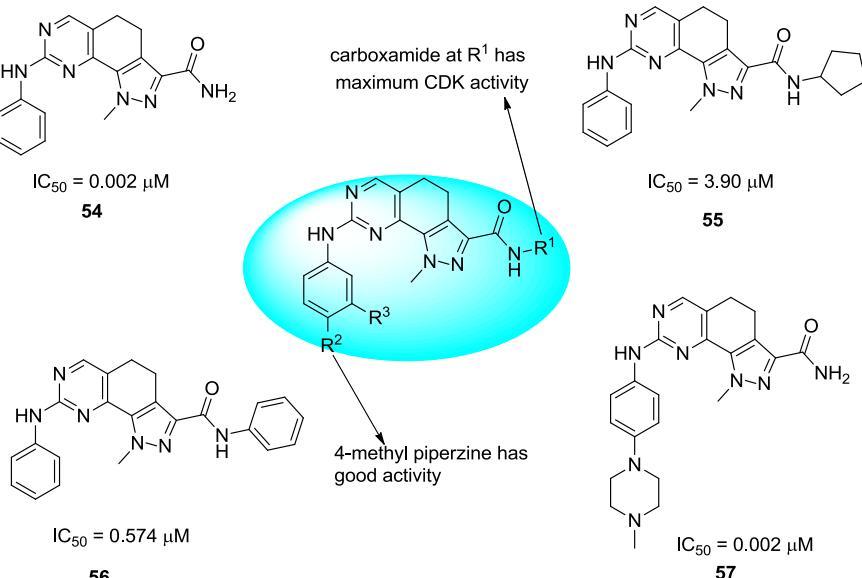
- Electron withdrawing groups are important for acting 3D-QSAR, including COMFA and COMSIA. Important interactions were seen with aspartate, arginine and glycine.

Fig. 15. Docking interactions of 1-(2-hydroxyethyl)-8-((2-(2,2,2-trifluoroethyl)phenyl)amino)-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide (**53**) with Plk1.

4. Pyrazolo[5,1-*b*]quinazoline

4.1. Synthetic strategies

Literature search has revealed numerous synthetic strategies for the synthesis of pyrazolo[5,1-*b*]quinazolines which are represented Fig. 9. These are depicted in the following distinct routes: Ammar et al. synthesized pyrazolo[5,1-*b*]quinazoline derivatives by refluxing 3-(4-aryl)-2-cyano-N-(2-methoxycarbonylphenyl)

**Key points**

- Activity decreases by introduction of bulky group at R¹.
- Activity increases by introduction of 4-methylpiperazine-1-yl at R².

Fig. 16. SAR and IC₅₀ values of pyrazolo[4,3-*h*]quinazoline derivatives against cyclin dependent kinase.

acrylamides with NH₂NH₂ in *n*-butanol (route-a) [56]; Chen et al. reacted 2-amino-N-arylbenzohydrazide with alkynal diethyl acetal in the presence of CuBr and Cs₂CO₃ (route-b) [57]; Zhou et al. treated 2-amino-N-(1-arylethylidene)benzohydrazide with 10 mol % I₂ in the presence of triethyl orthoformate (route-c) [58].

4.2. Biological activities

The major biological activities portrayed by pyrazolo[5,1-*b*]quinazoline are discussed below:

4.2.1. Neurotrophin nerve growth factor antagonist

The neurotrophin nerve growth factor (NGF) [59,60] interacts with tyrosine kinase receptor (Trka) [61,62] and neurotrophin receptor p75^{NTR}. In 2004, Colquhoun reported that the nerve growth factor antagonist [7-(Benzylamino)-4,9-dihydro-4-methyl-9-oxo-pyrazolo[5,1-*b*]quinazoline-2-carboxylic acid; PD90780] (**42**) (Fig. 10) interacts with NGF. ¹²⁵I-NGF cross linked to Trka and p75^{NTR} in the presence of these antagonists. The inhibitory action of **42** on Brain-derived neurotrophic factor (BDNF) and NT-3 was high at increased concentrations and was very low or negligible at low concentrations [63].

Docking studies of derivative **43** to p75^{NTR} binding site of NGF using molecular modeling package of SYBYL 6.9 showed that the complex was stabilized by intermolecular ionic and H-bonding interactions. Hydrophobic interactions were also seen to be responsible for stability of complex. The carboxylic group of **43** showed interactions with Lys34 and Lys95. Carbonyl group interacted with Lys32, Lys34 and Arg100 by H-bonding. Phenyl ring showed π-π stacking interaction with Phe101 (Fig. 11).

4.2.2. Anti-allergic activity

Capiris et al. disclosed the anti-allergic activity [64] of pyrazolo[5,1-*b*]quinazoline-9-ones. Among the series of the compounds evaluated, 4, 9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (**44a**) emerged as an extremely potent compound. SAR studies revealed that on substituting methyl group

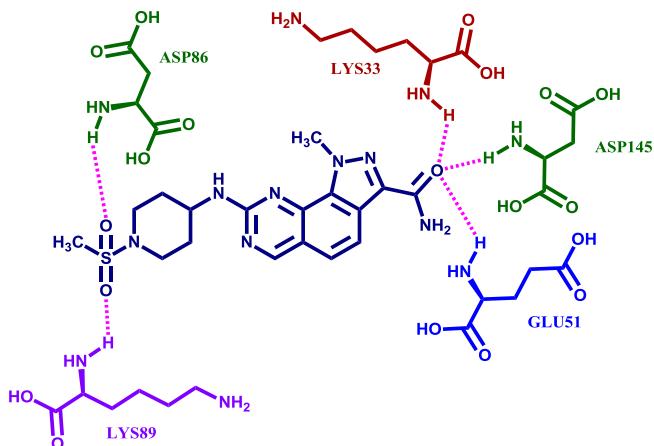


Fig. 17. Docking interactions of 1-methyl-8-((1-(methylsulfonyl)piperidin-4-yl)amino)-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (**58**) with cyclin dependent kinase.

at position-4, the activity of the compound escalates (**44b**) while substitution with benzyl group has an opposite effect. Substitution of hydroxyl groups at positions-5 and position-7 increased the activity considerably, especially for **44c** and **45a**. The dimethoxy analogs also showed escalation in potency (**45b**) (Fig. 12). The compounds were evaluated by passive cutaneous anaphylaxis (PCA) [65,66] reaction in rats for assessing the activity [67].

5. Pyrazolo[4,3-h]quinazoline

5.1. Synthetic methodology

In 2011, Caldarelli et al. reported the synthesis of pyrazolo[4,3-h]quinazoline derivatives (**47**; Fig. 13) from the reaction of enamines (**46**) in the presence of phenylguanidine carbonate at 110 °C [68].

5.2. Biological activities

Pyrazolo[4,3-h]quinazoline and derivatives exhibited various bioactivities which are discussed below.

5.2.1. Polo like kinase inhibitors (Plk1)

Beria et al. disclosed that 8-[(2-methoxy-5-(4-methylpiperazin-1-yl)phenyl)amino]-1-methyl-4,5-dihydro-1H-pyrazolo-[4,3-h]quinazoline-3-carboxamide (**48**) exhibits high potency and efficacy

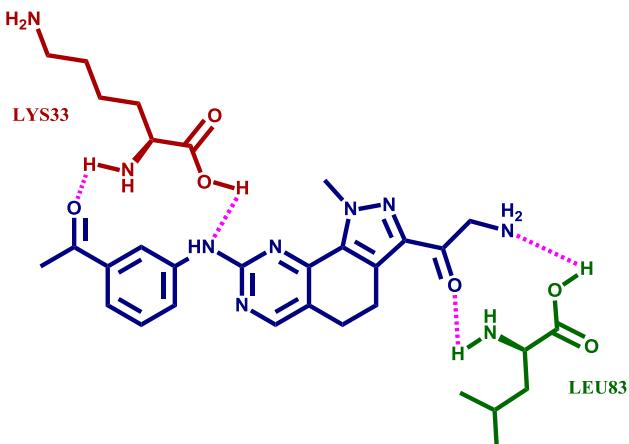
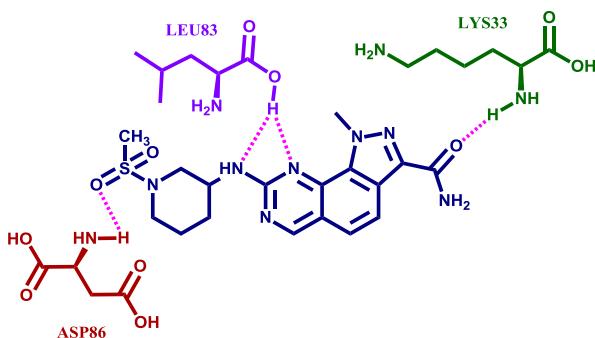


Fig. 18. Docking pose of 1-(8-((3-acetylphenyl)amino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-yl)-2-aminoethanone (**59**) with CDK2.



Key points

- Methyl sulfoxide group gives extra interactions with binding activity
- C-14 NH₂ group is optimum for activity.

Fig. 19. Binding interactions of **58** with residual amino acids of CDK2/CyclinA.

as ATP mimetic inhibitor of Plk1 [69,70]. Bulkier groups at position-1 decreased the activity against Plk1 (**49**), which was further decreased on introduction of ethyl ester, carboxylic acid or secondary amide at position-3 (**50**, **51** and **52**) (Fig. 14) [71]. The compounds of this class are under clinical trials; for example NMS-P937 is under phase 1 clinical trial [72].

In 2011, Lu et al. established combined molecular docking, structure based pharmacophore modeling and three-dimensional quantitative structure-activity relationship (3D-QSAR) studies on pyrazolo[4,3-h]quinazoline analogs as Plk1 inhibitors. They performed structure and ligand based alignment. The alignment was performed by GLIDE docking. Then COMFA (Comparative molecular field analysis) [73,74] and COMSIA (Comparative molecular similarity indices) [75–77] analysis were performed. The COMFA models obtained by pharmacophore-based method were found to be more superior ($q^2 = 0.628$ and $r^2 = 0.941$) to those obtained by GLIDE docking ($q^2 = 0.283$ and $r^2 = 0.420$). The pharmacophore model was reproduced by using SYBYL6.9. SAR revealed that medium sized substituents with hydrogen bond donor and acceptor interact with Asp194 and Lys82. Further, hydrophobic group with small size and strong electron-withdrawing atom interacts with Arg136 [78]. Some of these interactions of **53** with the receptor are summarized in Fig. 15.

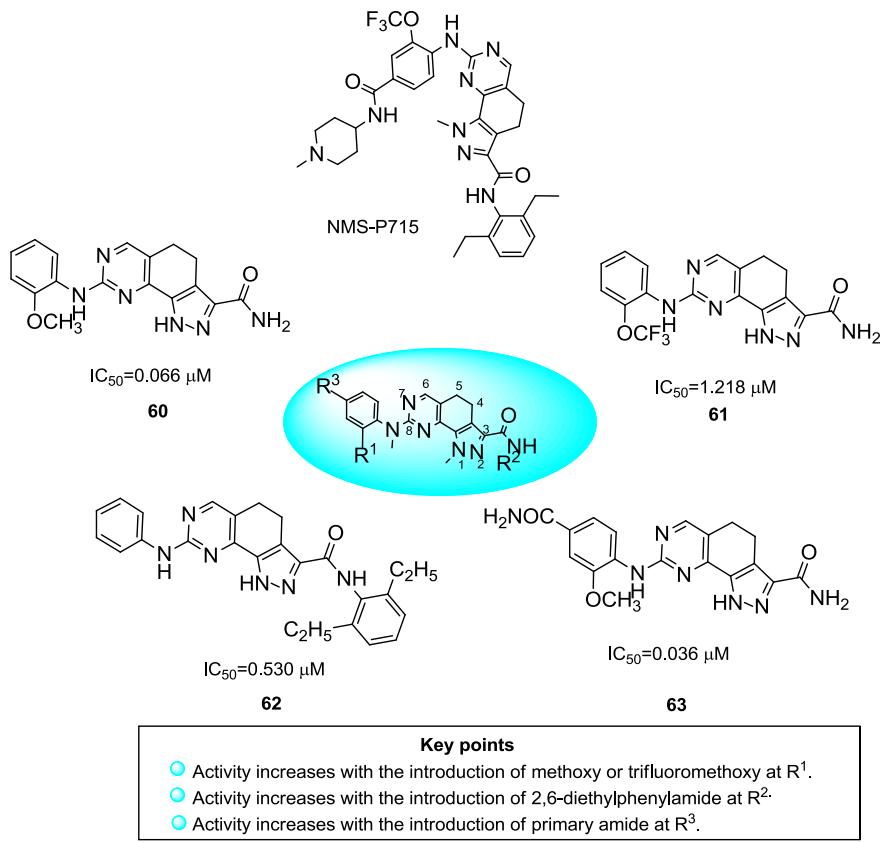
5.2.2. Cyclin Dependent Kinase (CDK) inhibitors

In 2009, Brasca et al. testified the CDK [79,80] inhibitory activity of pyrazolo[4,3-h]quinazoline-3-carboxamides [81]. The compounds exhibited remarkable anti-proliferative activity against A2780 human ovarian carcinoma cells and were active against CDKs. SAR studies (Fig. 16) highlighted that the compounds having primary carboxamide (R^1) moiety (**54**) displayed the maximum inhibition whereas the introduction of bulkier groups at R^1 decreased the CDK2 activity as in **55** and **56**. Some of the important SARs have been outlined in.

In 2011, Wang et al. performed 3D-QSAR modeling studies by using the molecular modeling package SYBYL6.9 and further analyzed binding site by using electrostatic maps analysis. Further



Fig. 20. Pyrazolo[4,3-h]quinazoline derivative.

**Fig. 21.** IC₅₀ values of MPS1 inhibitors.

MOE's (Molecular Operating Environment) [82,83] protonate 3D tool and volsurf analysis were used for molecular fragment replacement studies and ADME properties. The docking studies revealed that methylsulphonyl group of piperidine ring interacted with Asp86 and Lys89 by H-bonding and R¹ group interacted with Lys33, Glu51 and Asp145 [84]. The *in vivo* studies were found to be consistent with *in vitro* studies and carboxamide group was found

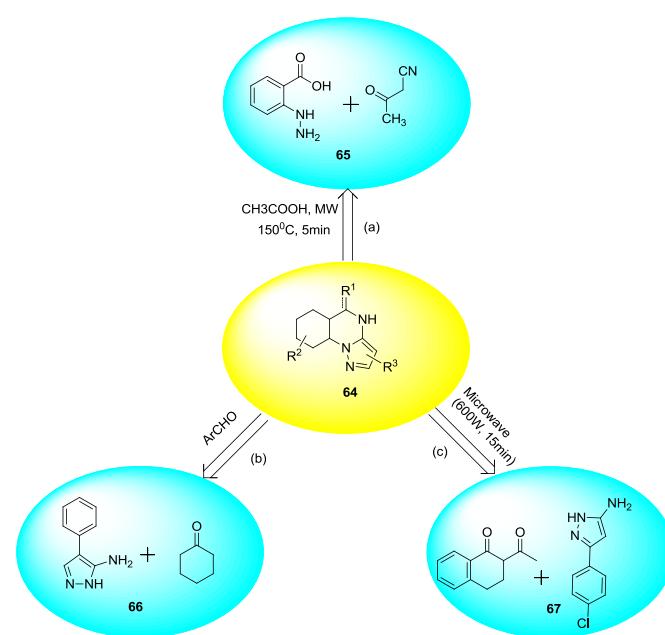
to be optimum for interaction and activity. The important interactions observed in case of **58** with CDK are highlighted in Fig. 17.

Ai et al. reported 4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline derivatives as potential inhibitor of CDK2/cyclin A. *In silico* studies were conducted on pyrazolo[4,3-*h*]quinazolines analogs as CDK2 inhibitors based on COMFA and COMSIA followed by molecular docking [82]. The compound 1-(8-((3-acetylphenyl)amino)-1-methyl-4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-yl)-2-aminoethanone was docked [85] and the docking results disclosed some of the important interactions of **59** with CDK2 which are summarized in Fig. 18.

In 2010, Lan et al. performed the 3D-QSAR and docking studies on a series of pyrazolo[4,3-*h*]quinazoline-3-carboxamides as CDK2/CyclinA inhibitors. The CoMFA and CoMSIA models gave r^2_{cv} values 0.644 and 0.507, q^2 values 0.959 and 0.951, respectively. 3D contour maps generated from the two models were applied to identify features important for the activity. Molecular docking, using MOLCAD, was employed to explore the binding mode between these compounds and the receptor. The N-9 and N-15 acted as the hydrogen bond acceptor and donor, formed H-bond with the –NH and –OH group of Leu83 residue, respectively. The carbonyl group at C-14 position formed H-bond with –NH₂ group of Lys33 residue. The methylsulfate group acted as a hydrogen bond acceptor by binding to the –NH group of Asp86 (Fig. 19). The results confirmed the observation from the CoMSIA hydrogen bond donor and acceptor contour maps [86].

5.2.3. Pim kinase inhibitor

In 2013, Casuscelli reported that pyrazolo[4,3-*h*]quinazoline derivative exhibit Pim kinase [87] inhibitory activity. The general chemical structure of the synthesized compounds is shown in Fig. 20 [88].

Fig. 22. Various retro-synthetic routes for pyrazolo[1,5-*a*]quinazoline and its derivatives.

Compound	R ¹	R ²	IC ₅₀ mGlu2 (μM)	IC ₅₀ mGlu3 (μM)
68			1.93	0.884
69			0.852	0.165
70			>10	>10
71			-4	0
72			2	39
73			7	19
74			8	28
75			245 nM	78 nM

Fig. 23. Pyrazolo[1,5-*a*]quinazoline derivatives as allosteric modulators.

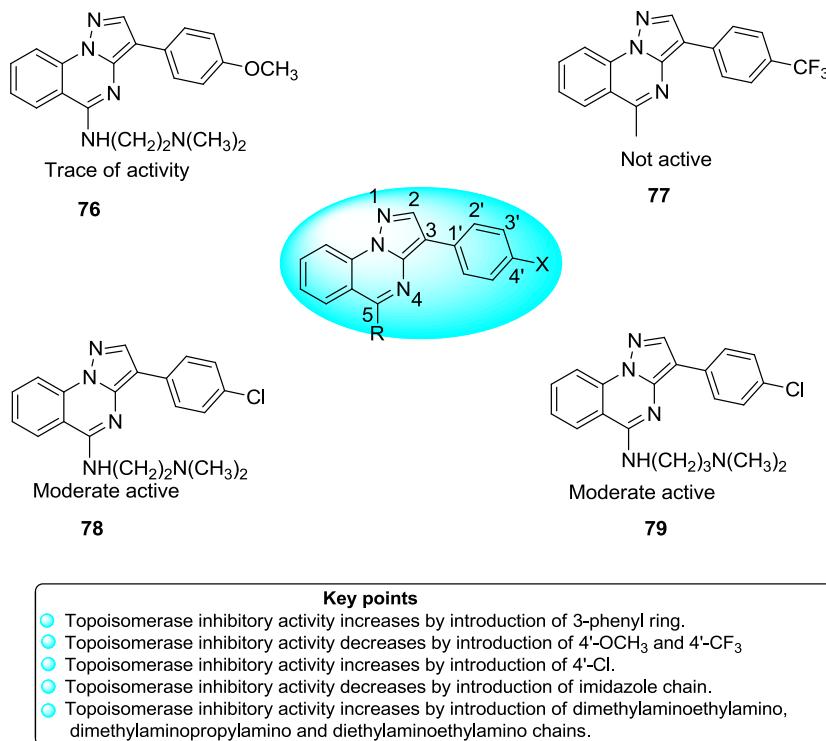
5.2.4. Monopolar Spindle-1 kinase (MPS1)inhibitor

In 2010, Colombo et al. characterized NMS-P715 [89] as a selective and orally bioavailable MPS1 [90] inhibitor. NMS-P715 selectively reduced cancer cell proliferation without effecting the normal cells [89]. In 2011, Caldarelli et al. confirmed and reported 4,5-dihydro-pyrazolo[4,3-*h*]quinazoline-3-carboxamides as MPS1 inhibitors. SAR studies revealed that methoxy group at R¹ increased MPS1 inhibitory potency (**60**) and trifluoromethoxy at R¹ (**61**) increased the potency. Selectivity was increased with substitution of diethylphenylamide at R² (**62**) whereas primary amide at R³ increased the activity of the compound (Fig. 21). The effectiveness of the compounds was assessed and measured as tumor growth inhibition in xenograft mouse models [91] (**63**) [68].

6. Pyrazolo[1,5-*a*]quinazoline

6.1. Synthetic strategies

Orvieto et al. synthesized pyrazolo[1,5-*a*]quinazolines (**64**) by the reaction of 2-hydrazinylbenzoic acid with 3-oxoalkanenitrile in the presence of CH₃COOH in microwave at 150 °C (route-a) [92]. Petrov et al. disclosed the three-component reaction of 3(5)-amino-4-phenylpyrazole with aromatic aldehydes and cyclohexanone in acetic acid to give (**64**) (route-b) [93]. Low et al. established microwave synthesis of (**64**) from 2-acetal-3,4-dihydronaphthalen-1(2H)-one and 3-(4-chlorophenyl)-1*H*-pyrazolo-5-amine (route-c) (Fig. 22) [94].

**Fig. 24.** SAR of topoisomerase-1 inhibitors.

6.2. Biological activities

Pyrazolo[1,5-*a*]quinazoline derivatives' bioactivities have been disclosed below.

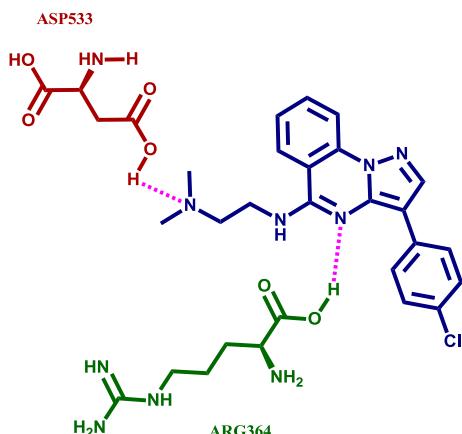
6.2.1. Metabotropic glutamate receptors/negative allosteric modulator(mGlu2/mGlu3 NAMs)

In 2014, Wentur et al. reported pyrazolo[1,5-*a*]quinazoline-5(4H)-ones [95] as negative allosteric modulators of metabotropic glutamate receptors [96–98] through single point assay. From SAR studies (Fig. 23) it was observed that the presence of 3-sulfonamidephenyl (68) or 3-pyridyl (69) at R² led to an increase in activity than the compounds with phenyl substitution (70) or p-methoxy phenyl (71). Replacement of phenyl at R¹ with 3-fluoro phenyl decreased the potency towards mGlu2 and mGlu3 (72). Similarly, increasing the size of halogen also decreased the potency as in 73 and 74. The compound 4-methyl-2-phenyl-8-(pyrimidine-

5-yl)pyrazolo[1,5-*a*]quinazoline-5(4H)-one (75) emerged as the most important inhibitor with nanomolar range of IC₅₀ at 245 against mGlu2 and 78 against Glu3.

6.2.2. Topoisomerase inhibitors

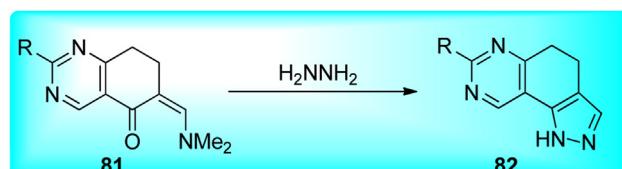
Taliani et al. disclosed the topoisomerase-1 inhibitory activity [99] of phenylpyrazolo[1,5-*a*]quinazoline-5(4H)-one [100]. From SAR studies (Fig. 24) it has been revealed that the topoisomerase-1 inhibitory activity can be increased by substituting 3-phenyl ring. Substitution of 4'-OCH₃ and 4'-CF₃ showed poor activity (76 and 77) and 4'-Cl substitution escalated the activity (78 and 79). More rigid and less basic groups like imidazole containing chain exhibited very poor activity (77). Dimethylaminoethylamino, dimethylaminopropylamino and diethylaminoethylamino chains imparted good activity (78 and 79). From docking studies it was revealed that N atom interacts with Arg364 through H-bonding and dimethylamino moiety interacts with Asp533 (Fig. 25).

**Fig. 25.** Docking interactions of N-(3-(4-chlorophenyl)pyrazolo[1,5-*a*]quinazoli-5-yl)-N,N-dimethylethane-1,2-diamine (80) with topoisomerase-1.

7. Pyrazolo[3,4-*f*]quinazoline

7.1. Synthetic strategy

Tonkikh et al. synthesized dihydropyrazolo[3,4-*f*]quinazolines (Fig. 26) by reacting 6-dimethylamino-5-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline with hydrazine [101].

**Fig. 26.** Synthesis of pyrazolo[4,3-*h*]quinazolines.

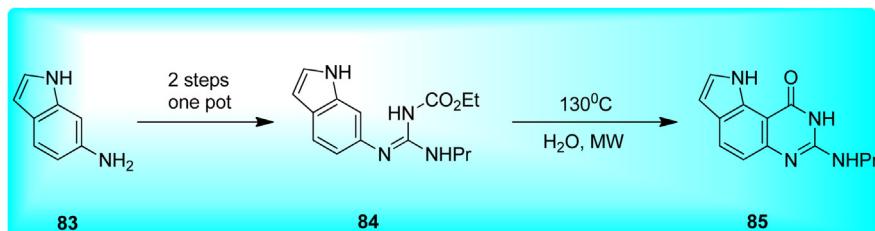


Fig. 27. Synthesis of pyrazolo[4,3-f]quinazoline derivatives.

Though the synthesis of pyrazolo[3,4-f]quinazolines has been reported no biological activity of this class is disclosed yet.

8. Pyrazolo[4,3-f]quinazoline

8.1. Synthetic strategy

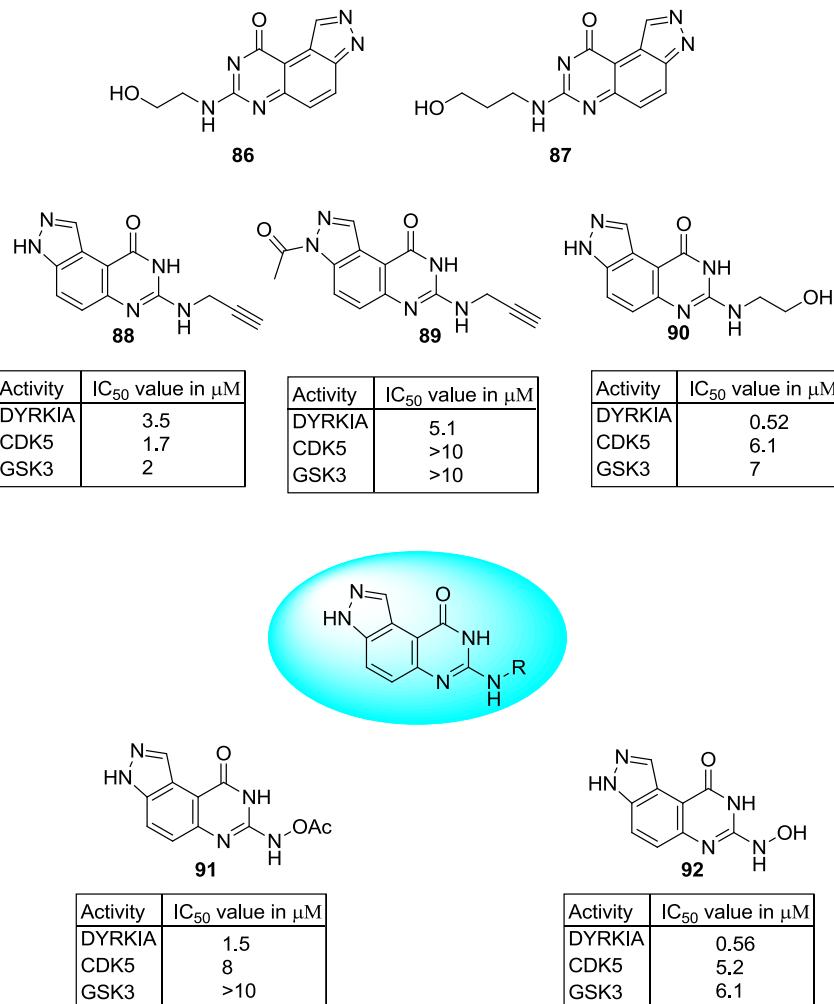
Debray et al. gave a catalyst-free one pot microwave synthesis of pyrazolo[4,3-f]quinazolines derivatives (Fig. 27) involving the

thermolysis of *N*-(hetero) arylguanidines (**85**) at 130 °C in water [102].

8.2. Biological activities

8.2.1. Dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) and CLK1 antagonist

These kinases play a very crucial role in cancer and neuronal disorders such as Alzheimer. 7-(2-hydroxyethylamino)-(**86**) and 7-



Key points

- Activity decreases by *N*-acylation of pyrazole ring.
- Potency decreases on acylation of 2-hydroxyethylamino.
- Selectivity changes on changing the length of substitution.

Fig. 28. DRK1A and CLK1 inhibitors.

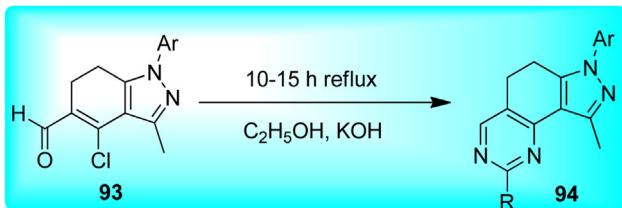


Fig. 29. Synthesis of pyrazolo[5,4-*h*]quinazoline derivatives.

(3-hydroxypropylamino)-pyrazolo[4,3-*f*]quinazolin-9-ones (**87**) observed to be the most active molecules to inhibit DYRK1A [**103,104**] and CLK1 [**105,106**]. Upon *N*-acylation of the pyrazolo ring, the activities against CDK5 (Cyclin Dependent Kinase 5) [**107**] and GSK3 (Glycogen Synthase Kinase 3) [**108**] decrease (**88** and **89**). Furthermore, the acylation of 2-hydroxyethylamino substituent also decreases the potency. By increasing the length of substituent there is a great effect on the selectivity (**90** and **91**) (Fig. 28). Kinase activities were assayed on DYRK1A, CDK5/p25, GSK-3 α / β , CK1 δ / ϵ , CLK1 (**90** and **92**) [**102**].

9. Pyrazolo[5,4-*h*]quinazoline

9.1. Synthetic strategy

Strakova et al. synthesized pyrazolo[5,4-*h*]quinazoline derivatives by refluxing chlorovinyl aldehydes with various guanidines in the presence of ethanol and KOH (Fig. 29) [109].

Though the synthesis of pyrazolo[5,4-h]quinazolines has been described biological activity of this compound has been not yet reported.

10. Patents covering pyrazoloquinazolines

In 1978, Vogt et al. filed patent on "pyrazolo[1,5-*c*]quinazoline derivatives and related compounds". The research group invented derivatives of pyrazolo[1,5-*c*]quinazolines having structure as shown in Fig. 30 [110].

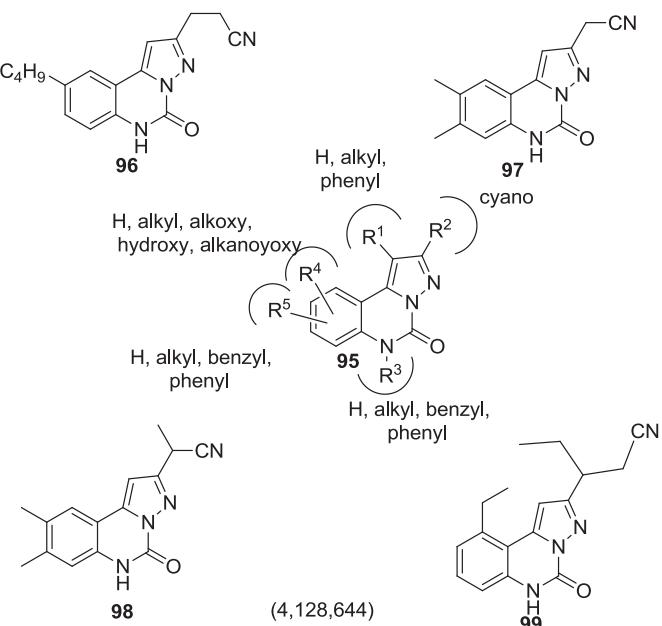


Fig. 30. Substituted pyrazolo[1,5-*c*]quinazolines derivatives.

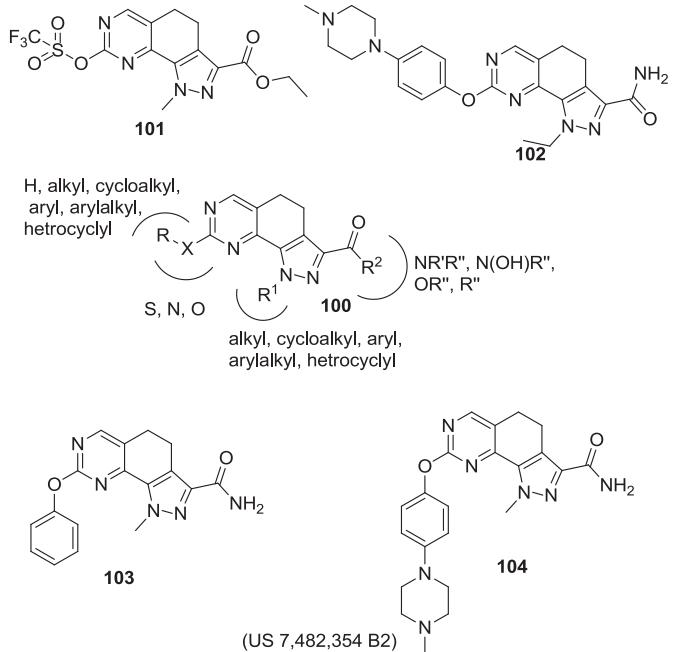


Fig. 31. Substituted pyrazolo[4,3-*h*]quinazolines derivatives patented by Traquandi et al.

In 2009, Traquandi et al. filed patent application on pyrazolo-quinazoline derivatives for their preparation and their use as kinase inhibitors. They synthesized pyrazolo[4,3-*h*]quinazoline derivatives and disclosed their activity against cancer and cell proliferation disorders. Some of their compounds are depicted in Fig. 31 [111].

In 2013, Caruso et al. patented substituted pyrazolo-quinazoline derivatives for their preparation and their use as kinase inhibitors. They synthesized substituted pyrazolo[4,3-*h*]quinazolines compounds (Fig. 32). They invented the compounds for the treatment of diseases caused by deregulation of protein kinase activity [112].

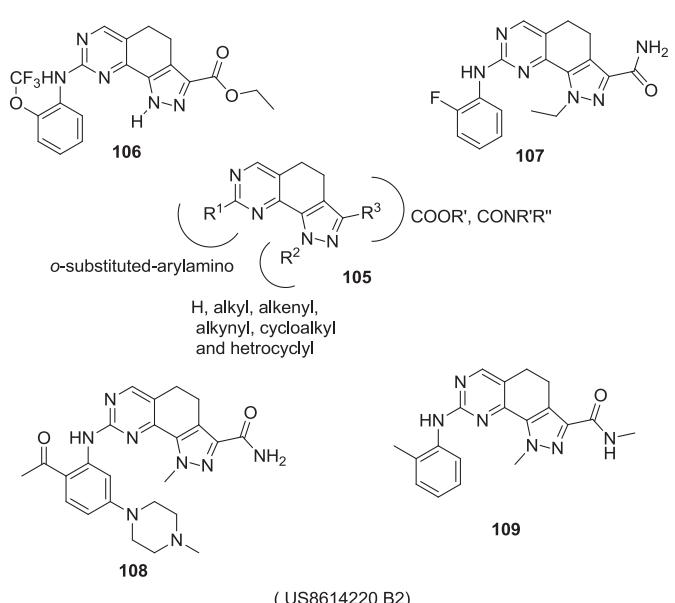


Fig. 32. Substituted pyrazolo[4,3-*h*]quinazolines derivatives patented by Caruso et al.

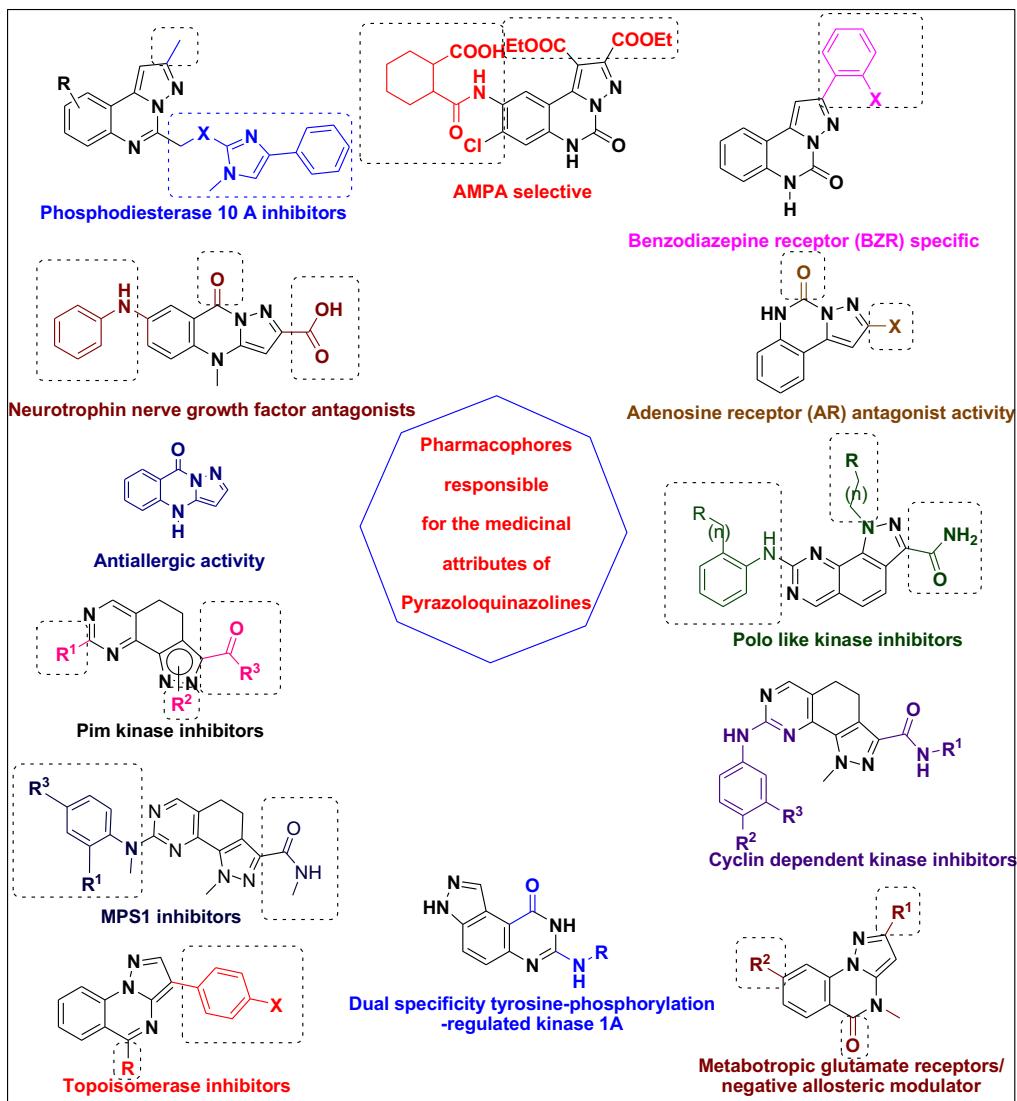


Fig. 33. Summary of pyrazoloquinazolines and their bioactivities.

11. Summary and conclusions

Literature survey on fused pyrazole and quinazoline scaffolds i.e. pyrazoloquinazolines disclosed important synthetic methodologies of each class of possible isomeric structures. In this review we have discussed and presented various methodologies involving use of conventional heating, microwave-irradiations, multi-component reactions (MCR) and metal-catalyzed reactions employed for the synthesis of several pyrazoloquinazolines. These synthetic approaches further offered the scope of developing a library of pyrazoloquinazolines having substitutions on the ring(s) for high throughput screening (HTS) of compounds.

Other than the mentioned synthetic expansions of pyrazoloquinazolines, the medicinal attributes portrayed by each class of the compounds are broad, encompassing benzodiazepine receptor agonistic, antimicrobial, anticancer, anti-allergic activities and many more (Fig. 33). The synthesized compounds of each class being heterocyclic in nature get accommodated and stabilized into the active site of the target receptor or enzyme such as topoisomerase-1, CDK, Plk-1, NFK, etc. through various interactions like *H*-bonding acceptor and/or donor, π - π stacking, and hydrophobic. NMS-P937 (1-(2-hydroxyethyl)-8-((5-(4-methylpiperazin-

1-yl)-2-(trifluoromethoxy)phenyl)amino)-4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide) is under phase 1 clinical trial for the treatment of solid tumors. The compiled results in this review on structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR) of pyrazoloquinazolines will help medicinal chemists to opt appropriate functional groups/substituents for fragment-based/structure-based drug designing of compounds. Further, X-ray co-crystallized pyrazoloquinazolines with target protein could provide some additional advantages for the rational design of agonists/antagonists.

We have also revealed some unknown classes of pyrazoloquinazolines which are either not yet explored for biological evaluation or not even been synthesized. This would encourage the researchers with the coveted opportunity to design, synthesize and generate libraries of the above mentioned unreported or unexplored classes of pyrazoloquinazolines for their development as medicinally active compounds.

Acknowledgments

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Abbreviations

QSAR: quantitative structure-activity relationship

PLK1: polo-like kinase 1

COMFA: comparative molecular field analysis

COMSIA: comparative molecular similarity index analysis

CDK: cyclin-dependent kinases

MOE: molecular operating environment

ADME: absorption, distribution, metabolism, and excretion

MPS1: monopolar spindle 1

IC₅₀: inhibitory concentration

DYRK1A: dual specificity tyrosine-phosphorylation-regulated kinase 1A

CLK1: CDC-like kinase 1

BDNF: brain-derived neurotrophic factor

NGF: nerve growth factor

AR: adenosine receptor

PDE10A: phosphodiesterase 10A

BZR: benzodiazepine receptors

AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

NMDA: N-methyl-D-aspartate receptor

Gly: glycine

DMSO: dimethyl sulfoxide