

**PYRROLOPYRAZINE CURRENT STRATEGIES IN PHARMACOLOGICAL
ACTIVITIES AND METHODS OF SYNTHESIS**

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Summary

Substituted pyrrolopyrazines and their hydrogenated analogs attract a growing attention of chemists and biologists as potential class of biologically active substances. For example, an intensive study of substituted pyrrolothienopyrazines revealed their high Antitumour activity. Alkaloids, such as Brevianamide, Barretin, Cambines, etc. contain fragments of substituted hydrogenated pyrrolopyrazines. Many of these compounds have antimicrobial and antiviral activity, including activity against the human immunodeficiency virus. Specific phytotoxins and selective herbicides are also found among these substances. However, so far this class of heterocycles remains poorly studied, apparently, because of a limited number of methods for their synthesis. This review discusses the structure-activity relationship of the most potent compounds. It can act as an important tool for medicinal chemists to develop newer compounds possessing pyrrolopyrazines moiety that could be better agents in terms of efficacy and safety.

Keywords: Biological activity, Pyrrolo pyrazine, SAR, Total Synthesis.

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Introduction

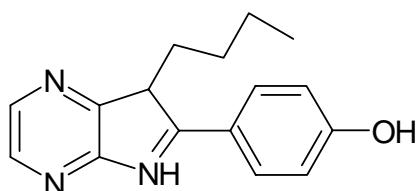
Pyrrolopyrazine is a bicyclic heterocycle possessing pyrrole condensed with pyrazine at [2, 3, b] position having general formula $C_6H_6N_3$. It has been studied extensively for its various biological activities mainly concern with the antidepressant activity, antiviral activity due to its structural resemblance with 5HT, Serotonin.



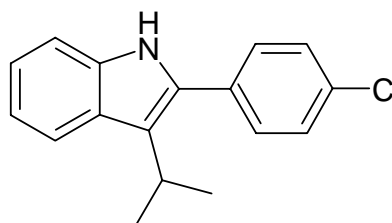
5H-pyrrolo[2,3-b]pyrazine

Antiproliferative activity

New derivatives of pyrrolo [2, 3-b] pyrazine were synthesized and tested on a panel of cultured human tumor cell lines. It was found that 6-amino-5-(3-chlorophenylamino)-7-(1-methyl-1H-benzo[d]imidazol-2-yl)-5H-pyrrolo[3,2-b]pyrazine-2,3-dicarbonitrile (4j) exhibited a significant antiproliferative activity: GI50 for cell lines RXF 393 (renal cancer) and BT-549 (breast cancer) were 14 and 82 nM, respectively. To identify possible molecular targets, docking of the most active compounds into the active sites of cyclin-dependent kinases was performed. Molecular modeling of the inhibitor–enzyme complexes showed the differences in the binding poses of new pyrrolo[2,3-b]pyrazine derivatives in the kinase ATP-binding site compared with known pyrrolo[2,3-b]pyrazine inhibitors called alosines. The patterns of drug kinase interactions correlated well with antiproliferative activities of novel derivatives.¹



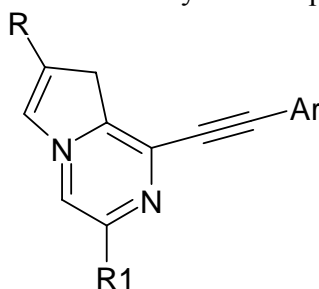
Alosine A



Alosine B

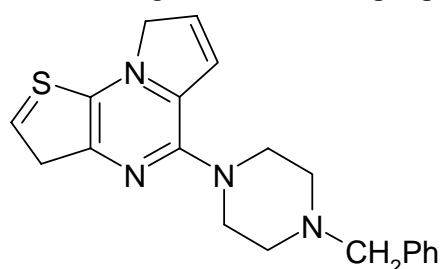
mGluR5 antagonists

The synthesis and the structure activity of a new series of pyrrolo [1, 2-a] pyrazine is reported. These molecules are potent and selective non-competitive mGluR5 antagonists and may shed new light on the pattern of substitution tolerated by this receptor.²



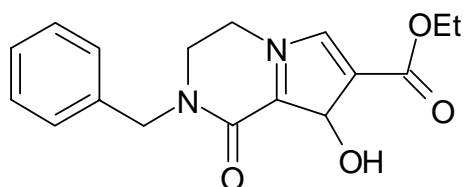
Serotonin-4 antagonists

Based on the definition of a 5-HT₄ receptor antagonist pharmacophore, a series of pyrrolo[1,2-a]thieno[3,2-e] and pyrrolo[1,2-a]thieno[2,3-e] pyrazine derivatives were designed, prepared, and evaluated to determine the properties necessary for high-affinity binding to 5-HT₄ receptors. The compounds were synthesized by substituting the chlorine atom of the pyrazine ring with various N-alkyl-4-piperidinylmethanols. They were evaluated in binding assays with [³H]GR113808 (1) as the 5-HT₄ receptor radioligand. The affinity values (K_i or inhibition percentages) were affected by both the substituent on the aromatic ring and the substituent on the lateral piperidine chain. A methyl group on the tricyclic ring produced a marked increase in affinity while an N-propyl or N-butyl group gave compounds with nanomolar affinities. Among the most potent ligands, 34d was selected for further pharmacological studies and evaluated in vivo. This compound acts as an antagonist/weak partial agonist in COS-7 cells stably expressing the 5-HT₄(a) receptor and is of great interest as a peripheral antinociceptive agent.³



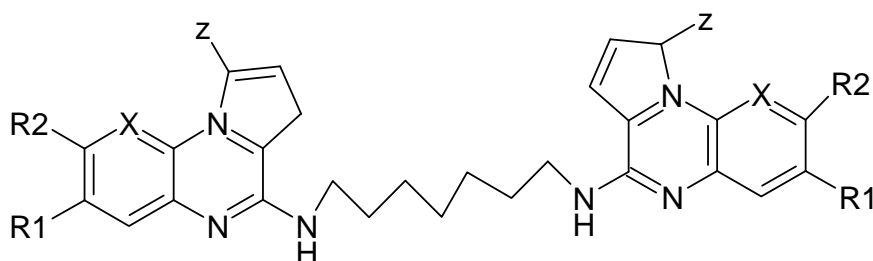
HIV-1 integrase inhibitors

A series of potent novel 8-hydroxy-3,4-dihydropyrrolo[1,2-a]pyrazine-1(2H)-one HIV-1 integrase inhibitors was identified. These compounds inhibited the strand transfer process of HIV-1 integrase and viral replication in cells. Compound 12 is active against replication of HIV-1 in cell culture with a CIC95 of 0.31 μM. Further SAR exploration led to the preparation of pseudosymmetrical tricyclic pyrrolopyrazine inhibitors 23 and 24 with further improvement in antiviral activity.⁴



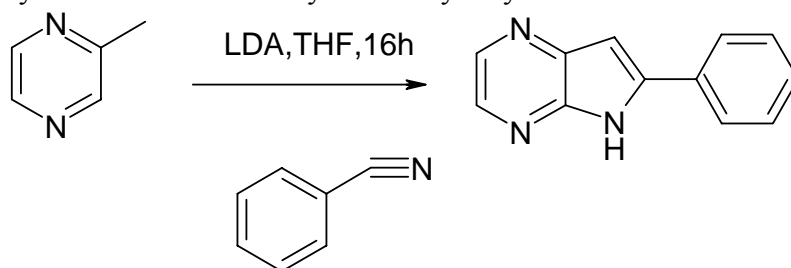
Antimalarial Activity

Three pyrrolo[1,2-a]quinoxalines, 15 bispyrrolo[1,2-a]quinoxalines, bispyrido[3,2-e]pyrrolo[1,2-a]pyrazines, and bispyrrolo[1,2-a]thieno[3,2-e]pyrazines were synthesized from various substituted nitroanilines or nitropyridines and tested for their in vitro activity upon the erythrocytic development of *Plasmodium falciparum* strains with different chloroquine-resistance status. Bispyrrolo[1,2-a]quinoxalines showed superior antimalarial activity with respect to monopyrrolo[1,2-a]quinoxalines. The best activity was observed with bispyrrolo[1,2-a]quinoxalines linked by a bis(3-aminopropyl)piperazine. Moreover, it was observed that the presence of a methoxy group on the pyrrolo[1,2-a]quinoxaline nucleus increased the pharmacological activity. Drug effects upon β-hematin formation were assayed and showed similar or higher inhibitory activities than CQ. A possible mechanism of interaction implicating binding of pyrroloquinoxalines to β-hematin was supported by molecular modeling.⁵

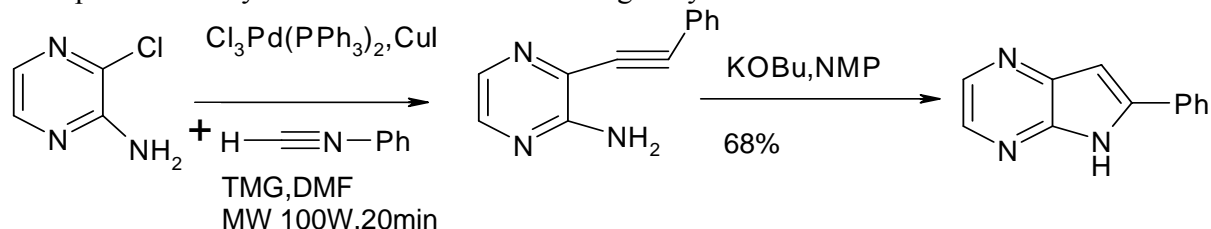


Methods of Synthesis

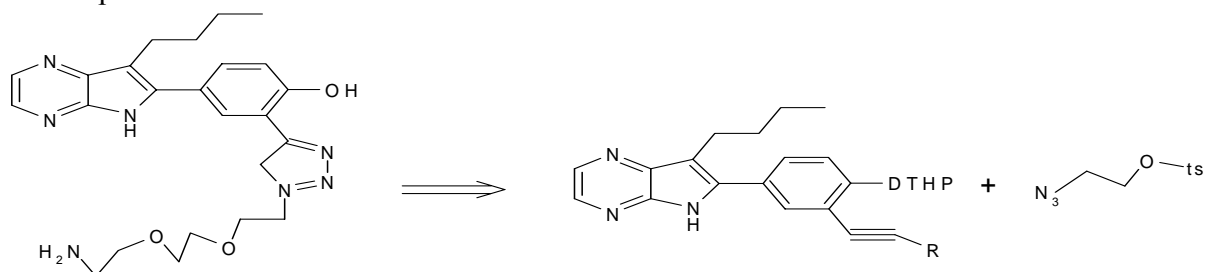
1. The efficient and convenient synthesis of 6-substituted-5H-pyrrolo[2,3-b]pyrazines. The reaction is a palladium-catalyzed heteroannulation process followed by deprotection to yield the desired pyrrolo[2,3-b]pyrazine substrates. The reaction starts with readily accessible N-(3-chloropyrazin-2-yl)-methanesulfonamide and commercially available terminal alkynes and works with aryl- and alkylalkynes.⁶



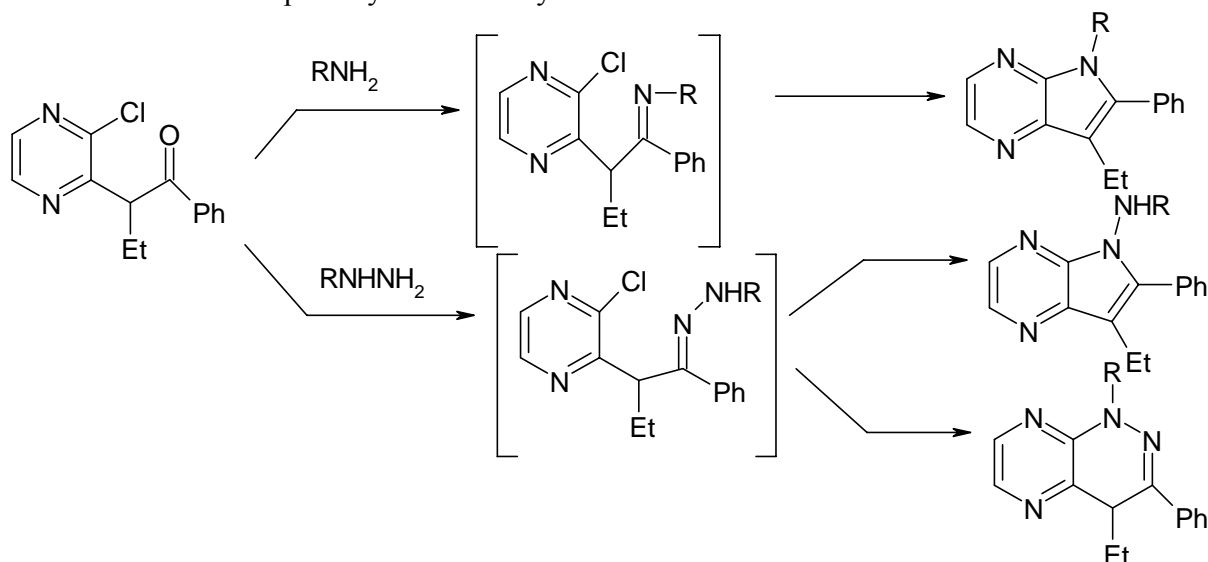
2. An improved synthesis of 6-substituted-5H-pyrrolo[2,3-b]pyrazines utilizing microwave heating. The reaction is a palladium-catalyzed heteroannulation process followed by deprotection to yield the desired substrates in good yield.⁷



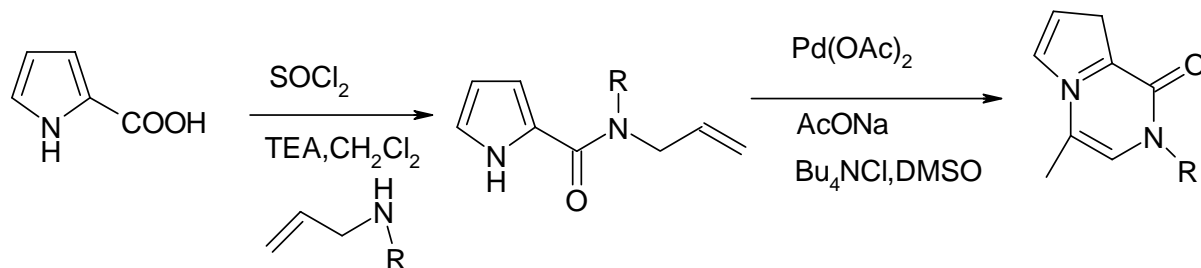
3. An efficient approach for the immobilization of a series of analogs of aloisine A, an in vitro inhibitor of protein kinases, to polymeric supports via a [3+2] cycloaddition reaction is reported.⁸



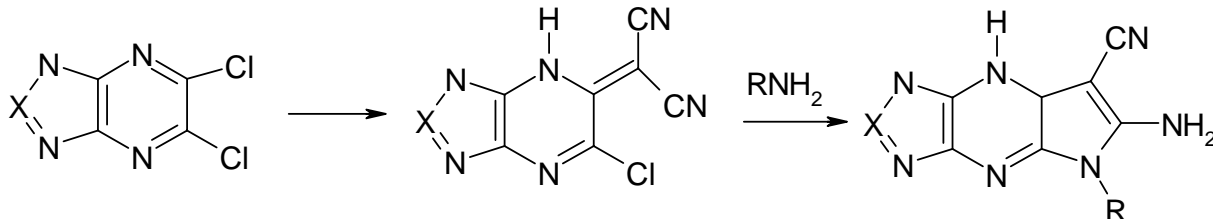
4. A highly efficient synthesis of the potent CDKs (cyclin-dependent kinases) inhibitors, aloisines (substituted 5H-pyrrolo[2,3-b]pyrazines) is presented. The method is based on highly selective monosubstitution of a single chlorine atom in 2,3-dichloropyrazine with lithiated ketones, esters, and nitriles followed by co-cyclization of the resulting intermediates with primary amines or hydrazines.⁹



5. Treatment of N-alkyl-N-allyl-pyrrolo-2-carboxamides with catalytic amounts of palladium derivatives gave regioselectively intramolecular cyclizations to generate bicyclic pyrrolo-fused structures. Pyrrolo[1,2-a]pyrazin-1-ones were achieved in high yields by an amination reaction, while pyrrolo[2,3-c]pyridin-7-ones and pyrrolo[3,2-c]pyridin-4-ones were obtained by an oxidative coupling process.¹⁰



6. The ylidene group installation/ring annulation sequence was applied to the synthesis of pyrrolo[2,3-b]pyrazines starting from monocyclic and heterocyclic fused halopyrazines.¹¹



Conclusion

The reviewed class of Pyrrolopyrazines a bicyclic heterocycles shows diverse biological activity such as antidepressant, antiviral, anticancer, antimalarial, herbicides etc. It can prove to be a promising lead for the medicinal chemist to develop new chemical entities with diverse biological activity. The Heterocycles can be synthesized using cycloaddition reaction and using

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