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Development of Novel Pyrazolopyridine and Pyrazolopyrimidine Frameworks: Synthetic Strategies

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تطوير مركّبات جديدة من البيرازولوبيريدين والبيرازولوبيريميدين: منهجيات التخليق العضوي

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Abstract:

This study reports the development of a new series of pyrazolo[4,3-b] pyridine and pyrazolo[1,5-a] pyrimidine derivatives designed as potential antischistosomal agents. A diverse set of fused nitrogen-containing heterocycles was successfully obtained and subjected to preliminary biological relevance assessment based on their structural features. These newly synthesized frameworks, belonging to scaffolds previously associated with notable antimicrobial and antiparasitic properties, demonstrate promising potential for further evaluation against *Schistosoma* species. The findings highlight the value of these heterocyclic systems as candidates for developing alternative therapies to complement existing schistosomiasis treatment strategies.

Keywords: Pyrazolopyridines; Pyrazolopyrimidines; Heterocyclic synthesis; Condensation reactions

الملخص

تُقدم هذه الدراسة تقريرًا عن تطوير سلسلة جديدة من مشتقات بيرازولو[4,3-b] بيريدين وبيرازولو[1,5-a] بيريميدين، المصممة كعوامل محتملة مضادة للبلهارسيا. وقد تم بنجاح الحصول على مجموعة متنوعة من الحلقات غير المتجانسة المدمجة المحتوية على النيتروجين، وخضعت لتقييم أولي لأهميتها البيولوجية بناءً على خصائصها البنيوية. تُظهر هذه الهياكل المُصنّعة حديثًا، والتي تنتمي إلى هياكل سبق ربطها بخصائص مضادة للميكروبات والطفيليات، إمكانات واعدة لمزيد من التقييم ضد أنواع البلهارسيا. تُبرز النتائج قيمة هذه الأنظمة الحلقية غير المتجانسة كنماذج أساسية لتصميم أدوية بديلة ضد الطفيلي المسبب للبلهارسيا.

الكلمات المفتاحية: بيرازولوبيريدينات؛ بيرازولوبيريميدينات؛ تخليق المركبات الحلقية غير المتجانسة؛ تفاعلات التكاثف

Introduction

Fused nitrogen-containing heterocycles that combine a pyrazole unit with a six-membered azine ring such as pyrazolo-pyridines and pyrazolo-pyrimidines represent an important class of 5:6 bicyclic systems. The coexistence of an electron-rich five-membered moiety and an electron-poor six-membered one grants these structures distinctive polarity and versatile electronic behavior. This unique arrangement enhances their chemical stability and enables wide structural modification, giving rise to numerous frameworks including pyrazolo[1,2-a] pyridines and pyrazolo[1,5-a] pyrimidines [1].

Because of their tunable reactivity and ease of functionalization, these fused pyrazoles occupy a central role in several fields such as drug development, photophysical research, industrial chemistry, and materials science. Among the notable members of this family are pyrazolo[3,4-b] pyridines, which have attracted scientific interest due to their diverse pharmacological properties; well-known examples include the anxiolytic compound **Tracazolate** and certain **N-acyl hydrazone** analgesics [2, 3].

Extensive literature also documents the considerable biological relevance of pyrazolopyrimidine derivatives [4-6]. For instance, pyrazolo[4,3-d] pyrimidines have been investigated as candidates for cancer therapy, inhibitors of phosphodiesterase, modulators of plant cytokinin pathways, anti-infective agents, and central nervous system regulators such as phosphodiesterase-5 inhibitors and adenosine receptor blockers [7-9]. They have additionally shown promising antimicrobial and anti-inflammatory effects, including inhibition of nitric-oxide formation triggered by LPS [10,11]. Likewise, derivatives belonging to the [3,4-d] subtype are reported to exhibit anticancer, anti-inflammatory, antituberculosis, antimicrobial, and antiviral activities [12-18]. The pyrazolo[1,5-a] pyrimidine series has also demonstrated notable anticancer potential in several studies [19-25] alongside other biological properties [26, 25-28].

Recent publications continue to emphasize the growing scientific interest in pyrazole-based fused heterocycles and their chemistry [29–31]. Among the biological activities associated with such systems, **antischistosomal effects** reported for specific pyrazolopyrimidines represent an especially important area of investigation.

In light of the diverse biological roles reported for pyrazolopyrimidine and pyrazolopyridine systems, particularly their emerging antischistosomal potential, the present work focuses on the design and synthesis of new fused pyrazole derivatives. The study involves the preparation of a series of pyrazolo[1,5-a] pyrimidine and pyrazolo[4,3-b] pyridine frameworks starting from functionalized pyrazole precursors. These newly obtained heterocycles are expected to provide valuable structural motifs for further biological evaluation, with the aim of identifying candidates possessing promising schistosomicidal activity.

Material and methods:

All melting point are uncorrected on a Griffin and George MBF010T (London) apparatus. Recorded yields correspond to the pure products. IR(KBr) spectra were recorded on a Perkin Elmer SP-880 spectrophotometer and ^{1}H-NMR spectra were measured on a Varian 270 MHz spectrometer in DMSO-d_6 as solvent and TMS as internal standard (chemical shifts are given as δ ppm). Microanalysis were carried out in the microanalytical data unit at Cairo and Mansoura universities.

6-Aryl-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazolo[4,3-b] pyridine-5-carbonitriles (7)

Method A:

A solution of (0.01 mol) and the arylidenes 3b, c (0.01 mol) in ethanol (50 ml) containing a catalytic of piperidine (0.1 ml), was heated under reflux for 3 hours then left to cool. The solid products so formed were collected by filtration, crystallized and then identified as 7.

Method B:

A mixture of 1 (0.01 mol) and 0.01 mol of 3e, f in ethanol (50 ml) were refluxed for 6 hours in presence of piperidine (0.3 ml). the solvent was concentrated to its half volume and left to cool. The solids deposited were filtered off, recrystallized and identified (m. p., mixed m. p.) as 7.

***6-(4-chlorophenyl)-1-methyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazolo[4,3-b] pyridine-5-carbonitrile (7a)*:** yellow crystals from ethanol, m. p. 251-253° C, yield 65%. IR (ν_{max} /cm^{-1}): 2228(conjugated CN), 1699(CO). ^{1}H-NMR(DMSO-d_6): (δ, ppm): 3.30(S, 3H, CH_3), 7.3-7.7(m, 10H, aromatic protons).

$C_{20}H_{13}ClN_4O$ (360.80): Calcd. C, 66.58; H, 3.63; N, 15.53%, Found C, 66. 78; H, 3.70; N, 15.23%.

1-methyl-6-(3-nitro-1H-pyrrol-2-yl)-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazolo[4,3-b] pyridine-5-carbonitrile (7b): Faint brown powder from ethanol/DMF, m. p. 300C, yield 70%. IR (ν_{max} /cm^{-1}): 2227(CN), 1675(CO). $C_{18}H_{12}N_6O_3$(360.33), Calcd. C, 60.00; H, 3.36; N, 23.32%, Found C, 60.08; H, 3.51; N, 23.36%.

(Z)-2,7-diamino-5-aryl-3-(m-tolyldiazenyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (8):

A solution of 5- amino pyrazole 2 (0.01 mol) in ethanol (50 ml) containing piperidine (0.1 ml) was treated with 3a, b (0.01 mol). The reaction mixture was refluxed for 3 hours and then left to cool. The resulting solid products were collected by filtration and crystallized from the proper solvent.

(Z)-2,7-diamino-5-phenyl-3-(m-tolyldiazenyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (8a): yellow crystals, from methanol, m. p. 291-293 ° C, yield 65%. IR (ν_{max} /cm^{-1}): 3604, 3572, 3470 (NH_2), 2215(conjugated CN),

1605(N=N). ^{1}H-NMR(DMSO-d_6): (δ, ppm): 2.35(s, 3H, CH_3), 7.12(s, 2H, NH_2), 7.34 -7.97(m, 3H, aromatic protons), 8.61(s, 2H, NH_2), 8.63(s, 2H, NH_2), $C_{20}H_{16}N_8$(368.40), Calcd. C, 65.21; H, 4.38; N, 30.42%, Found C, 65.33; H, 4.42; N, 30.35%.

(Z)-2,7-diamino-5-(4-chlorophenyl)-3-(m-tolyldiazenyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (8b): brown crystals, from ethanol, m. p. 250-252° C, yield 67%. IR (ν_{max}/cm^{-1}): 3580, 3460, 3302 (NH_2), 2215(conjugated CN), 1615(N=N). $C_{20}H_{15}ClN_8$(402.85), Calcd. C, 59.63; H, 3.75; N, 27.82%, Found C, 59.51; H, 3.67; N, 27.68%.

(E)-2,7-diamino-3-(m-tolyldiazenyl) pyrazolo[1,5-a] pyrimidine-6-carbonitrile (10):

A solution of (0.01 mol) in ethanol (50 ml) was treated with (0.01 mol) of 4d and two drops of piperidine, was refluxed for 3 hours and then left to cool at room temperature. The precipitate separated on cooling was filtered off and crystallized from ethanol to give yellow crystals 10, m. p.>300° C, yield 70%. IR (ν_{max}/cm^{-1}): 3422, 3273, 3200 (NH_2), 2214(conjugated CN), 1640(C=N), 1605 (N=N). ^{1}H-NMR(DMSO-d_6): (δ, ppm): 2.38(s, 3H, CH_3), 7.21(s, 2H, NH_2), 7.15 -7.60(m, 3H, aromatic protons), 7.96(s, 1H, aromatic protons), 8.42(s, 1H, pyrimidine H-5), 8.63(s, 2H, NH_2). $C_{14}H_{12}N_8$(292.31), Calcd. C, 57.53; H, 4.14; N, 38.33%, Found C, 57.23; H, 4.70; N, 38.30%.

Formation of pyrazolo[1,5-a] pyrimidine derivatives (15)

A mixture of 2 (0.01 mol) and 13 (0.01 mol) in ethanol (50 ml) containing acetic acid (1 ml) was refluxed for one hour. The deposited solid was collected by filtration and crystallized from the proper solvent to give 15.

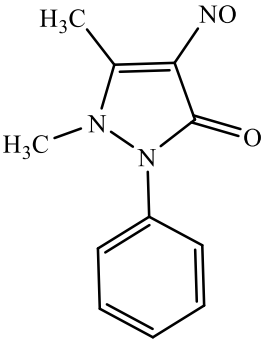
(E)-6-(1H-benzo[d]imidazol-2-yl)-3-((4-chlorophenyl) diazenyl) pyrazolo[1,5-a] pyrimidine-2,7-diamine (15a): red crystal from acetic acid, m. p.> 300° C, yield 75%. IR (ν_{max}/cm^{-1}): 3480, 3410, 3316 (NH_2), 2214(conjugated CN), 1605 (N=N). ^{1}H-NMR(DMSO-d_6): (δ, ppm): 7.33(s, 2H, NH_2), 7.21(s, 2H, NH_2), 7.50 -8.88 (m, 8H, aromatic protons), 8.59(s, 1H, pyrimidine H-5), 8.99(s, 2H, NH_2), 9.75(s, 1H, NH). $C_{19}H_{14}ClN_9$(403.83), Calcd. C, 65.51; H, 3.49; N, 31.22%, Found C, 56.50; H, 3.80; N, 31.34%.

(E)-6-(1H-benzo[d]imidazol-2-yl)-3-(m-tolyldiazenyl) pyrazolo[1,5-a] pyrimidine-2,7-diamine (15b): brown powder from ethanol/DMF, m. p. 265-267° C, yield 70%. IR (ν_{max}/cm^{-1}): 3418, 3356, 3273 (NH_2), 2214(conjugated CN), 1620 (N=N). $C_{20}H_{17}N_9$(383.42), Calcd. C, 62.65; H, 4.47; N, 32.88%, Found C, 62.45; H, 4.36; N, 32.79%.

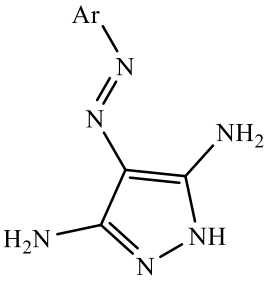
Results and discussion

In this study, a series of newly synthesized pyrazolo[1,5-a] pyrimidine and pyrazolo[4,3-b] pyridine derivatives were prepared as potential antischistosomal candidates. The synthetic pathway employed **4-nitroso-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (1)** together with **4-arylazo-5-aminopyrazoles (2)** as the principal starting materials. Compound **1** was found to undergo smooth condensation with arylidene malononitriles **3b, c** in ethanolic media containing catalytic piperidine, affording products formed through successive elimination of hydrogen cyanide and water. Spectroscopic evidence including elemental analysis, mass spectra, and IR supported the assignment of the reaction product as the pyrazolo[4,3-b] pyridine derivative **7**, particularly due to the presence of characteristic cyano and antipyrinyl carbonyl absorptions and the absence of an amino stretching band.

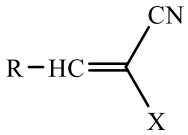
Comparable derivatives were also obtained when compound **1** reacted with ethyl α-cyano cinnamates **3e, f**, which proceeded through the loss of carbon monoxide, ethanol, and water. The formation of compound **7** was rationalized through initial nucleophilic addition of the methyl group in **1** to the activated C=C bond in **3**, generating adduct **4**, followed by ring closure to **5** and subsequent elimination (HCN or ethyl formate) to produce intermediate **6**, which aromatized to **7** after dehydration (Scheme 1).



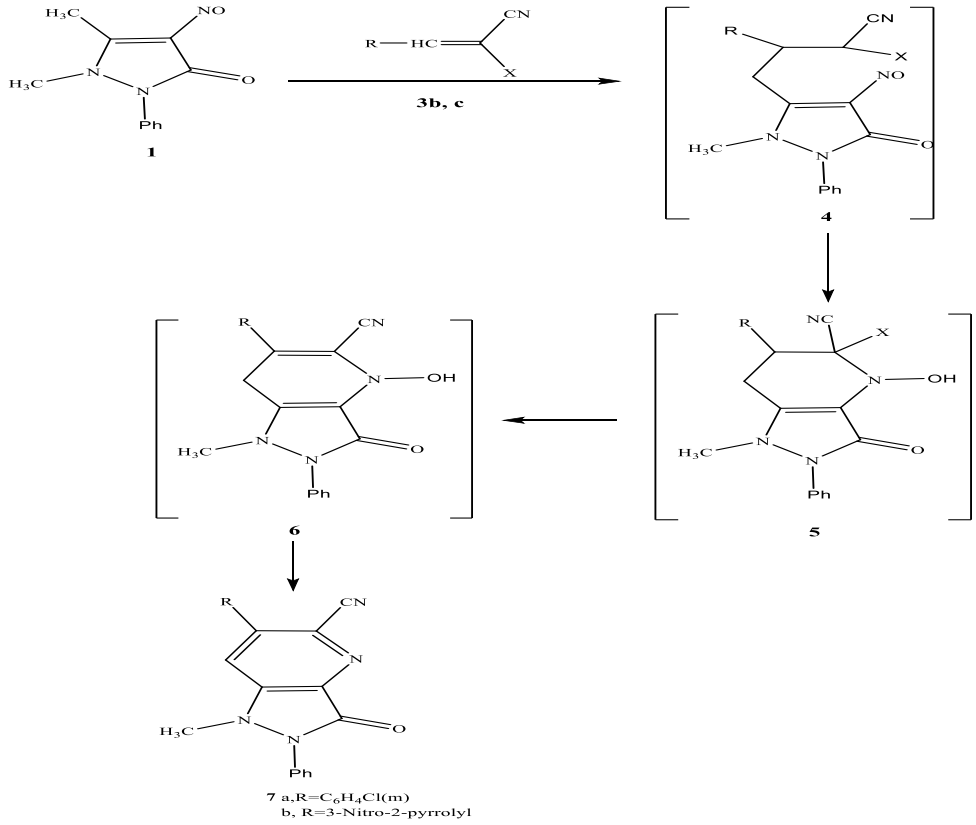
1



2



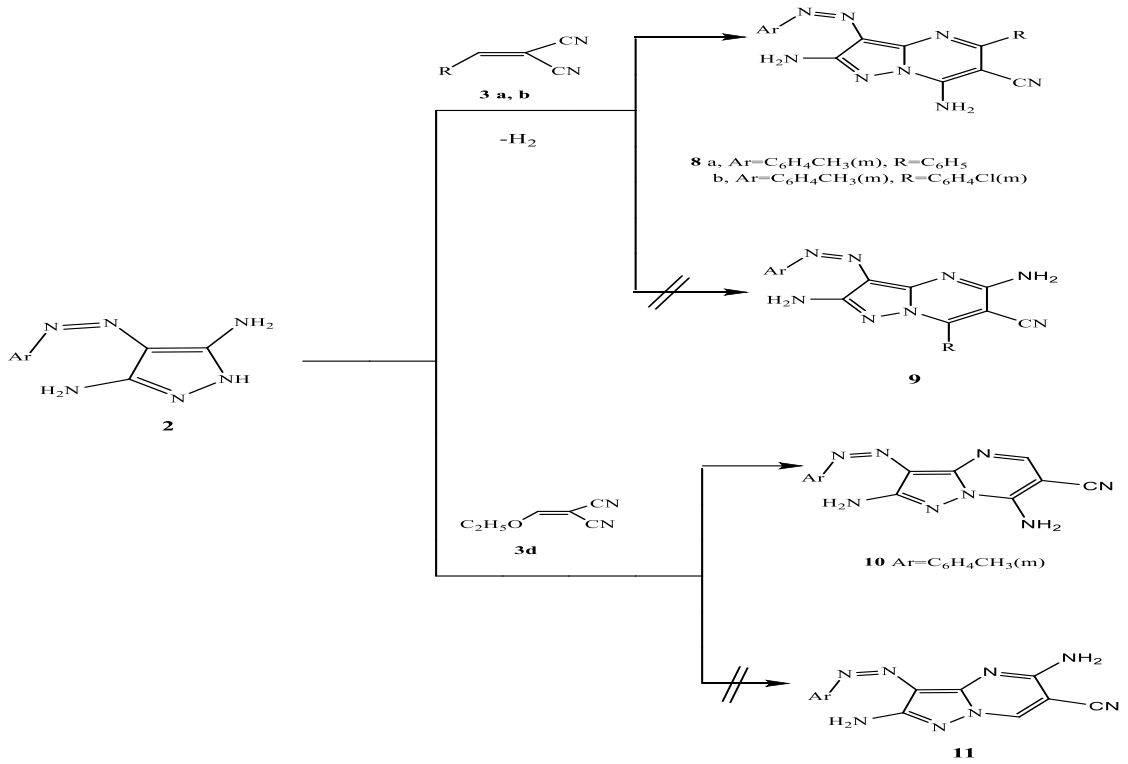
3 a, R=C_6H_5 ,X=CN
b, R=C_6H_4Cl(m) ,X=CN
c, R=3-Nitro-2-pyrrolyl ,X=CN
d, R=OC_2H_5 ,X=CN
e, R= C_6H_4Cl(m) ,X=$CO_2C_2H_5$
f, R=3-Nitro-2-pyrrolyl ,X=$CO_2C_2H_5$



Scheme 1

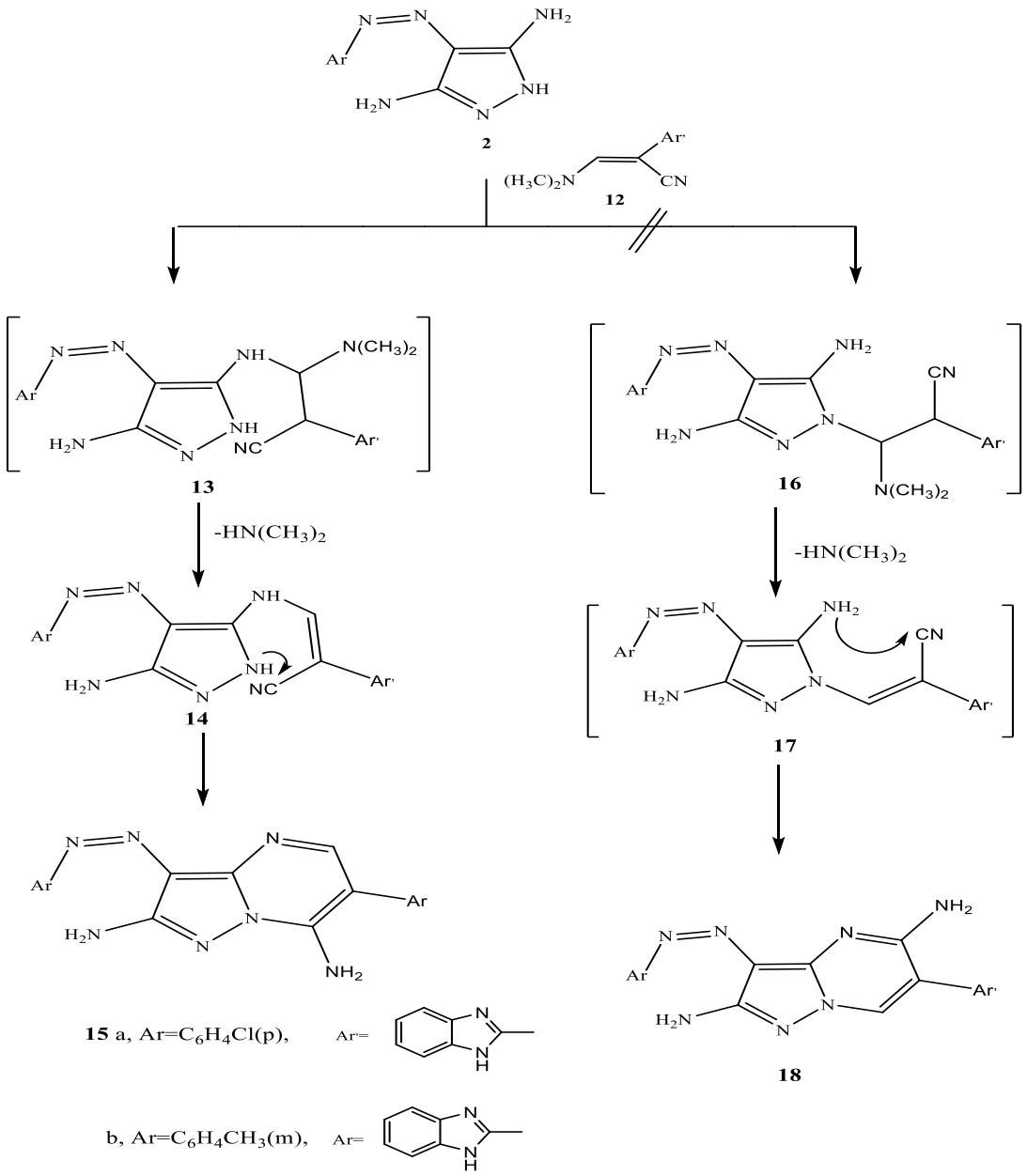
Similarly, the interaction of 5-aminopyrazoles **2** with arylidene malononitriles **3a, b** in ethanolic piperidine generated products for which several structural alternatives were initially considered. Acyclic formulations were ruled out based on IR spectra that showed only a single cyano absorption band. Furthermore, ^{1}H-NMR analysis revealed an amino resonance above δ 7.0 ppm, supporting the assignment of **7-aminopyrazolo[1,5-a] pyrimidines (8)**. Had the isomeric structure **9** been formed, the amino protons would have appeared at the typical aliphatic region (δ ≈ 4–6 ppm), consistent with previously observed anisotropic deshielding effects in similar pyrazolopyrimidines [32, 33]. Formation of **8** likely proceeds via nucleophilic attack by the exocyclic amine of **2** on the electron-deficient β-carbon of **3**, followed by intramolecular addition of the pyrazole nitrogen to the cyano group to generate the fused pyrimidine system.

Reaction of the aminopyrazoles **2** with ethoxymethylene malononitrile **3d** in ethanol/piperidine also yielded condensation products through loss of ethanol and hydrogen. The resulting compound could theoretically correspond to either **7-aminopyrazolo[1,5-a] pyrimidine (10)** or **5-aminopyrazolo[1,5-a] pyrimidine (11)**. The ^{1}H-NMR spectrum, however, revealed the amino signal near δ 7.2 ppm, a chemical shift consistent with structure **10**, whereas structure **11** would be expected to give considerably higher-field resonances (δ 4–6 ppm) as reported in earlier studies [32, 33]. A plausible mechanism involves nucleophilic displacement of the ethoxy group in **3d** by the exocyclic amine of **2**, followed by intramolecular addition of the pyrazole NH to the cyano group to furnish **10** (**Scheme 2**).



Scheme 2

Enamines are widely recognized as versatile intermediates in heterocycle construction [30, 34–36]. Extending our investigation in this direction, the reactivity of aminopyrazoles **2** toward the enamino nitrile **12**, namely ***3-(N, N-dimethylamino)-2-(benzimidazol-2-yl) prop-2-enenitrile***, was explored. Condensation of **2** with **12** in refluxing ethanol containing acetic acid afforded a product that could, in principle, correspond to **7-aminopyrazolo[1,5-a] pyridines (15)** or **5-aminopyrazolo[1,5-a] pyridines (18)**. The ^{1}H-NMR data supported structure **15**, despite the higher inherent nucleophilicity of the endocyclic imino nitrogen, which is sterically restricted. The reaction appears to proceed through initial attack of the exocyclic amine on the C=C bond of **12**, followed by elimination of dimethylamine and intramolecular cyclization via addition of the pyrazole NH to the cyano group, yielding the fused heterocyclic system **15** (**Scheme 3**).



Scheme 3

Conclusion

In summary, a new series of pyrazolo[4,3-b]pyridine and pyrazolo[1,5-a]pyrimidine derivatives were successfully developed, demonstrating the versatility of fused nitrogen heterocycles as scaffolds for medicinal chemistry. The structural diversity achievable through simple modifications highlights their synthetic utility and potential for biological optimization. Given the limitations of current antischistosomal therapies, these novel derivatives represent promising candidates for further pharmacological evaluation. The findings provide a solid foundation for future studies aiming to correlate molecular architecture with antiparasitic activity and to advance these frameworks toward the discovery of alternative therapeutic leads.

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