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Heterocyclic Synthesis Via Enaminonitriles: One-Pot Synthesis of Some New Pyrazole, Pyrimidine, Pyrazolo[1,5-A]Pyrimidine and Pyrido[2,3-D]Pyrimidine Derivatives

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Abstract A simple route for the synthesis of 5-aminopyrazole derivatives (9) was described through the readily accessible acrylamide derivative (7). Reaction of the aminopyrazole with different reagents such as α,β-unsaturated nitriles afforded pyrazol[1,5-a]pyrimidine (13,15,18). The structure of the enaminonitrile (6) was studied with different reagents such as thiourea and 2-thioxo-(1H)-pyrimidine-4-one (36) afforded pyrimidinethione derivative (35) and the pyrido[2,3-d]pyrimidine derivative (41), respectively.

Keywords DMF-DMA, 5-Aminopyrazole, Enaminonitrile, Thiourea and Pyrimidine

1. Introduction

Pyrazolo[1,5-a]pyrimidine are of considerable chemical and pharmacological importance as purine analogs and many derivatives of pyrazolo[1,5-a]pyrimidines have been reported to exhibit cyotoxic activity[1-9]. Several 7-substituted pyrazolo[1,5-a]pyrimidine derivatives were reported to have antiproliferative activity against HCT116 and other cell lines (e.g. compounds 1-3)[3,6,8] (figure 1).

Also, almost high percentage of adults between ages 40-70 suffer from insomnia at least one time during their lives. The drug Zaleplon (4)[10-13] has been found to be efficient in the treatment of sleep disorder where difficulty in falling asleep is the primary issue. Unlike many other hypnotic drugs, this substance does not interfere with sleep architecture and can be administered for up to five weeks without the risk of dependence or rebound insomnia upon discontinuation. Indiplon (5)[10, 14] has recently been released for use for the same purpose while the developments of Ocinaplon (6)[15], which is an anxiolytic drug in the pyrazolopyrimidine family of drugs, has been discontinued owing to liver complications observed in clinical trials. As a result, a need exists for the development of analogs of (1-6). (figure 1).

The present work comprises the combination of benzimidazole pharmacophore with various substituted aromatic or heterocyclic rings via carboxamides linker. It was interesting to synthesis hybrids possessing biological and pharmacological activities due to benzimidazole[16-29] and certain substituted pyrazoles[30-44] hoping that this combination may possess a potential analgesic activity along with possible anticancer effect.

In connection with our previous studies[45-53] and in view of utilizing the cyan-oacetamide as highly versatile intermediates for the construction of functionlized pyrazole, pyrimidinethione pyrazolopyrimidine and pyridopyrimidine derivatives of expected potential biological activity and excellent pharmacology encouraged us to synthesis novel entitled derivatives.

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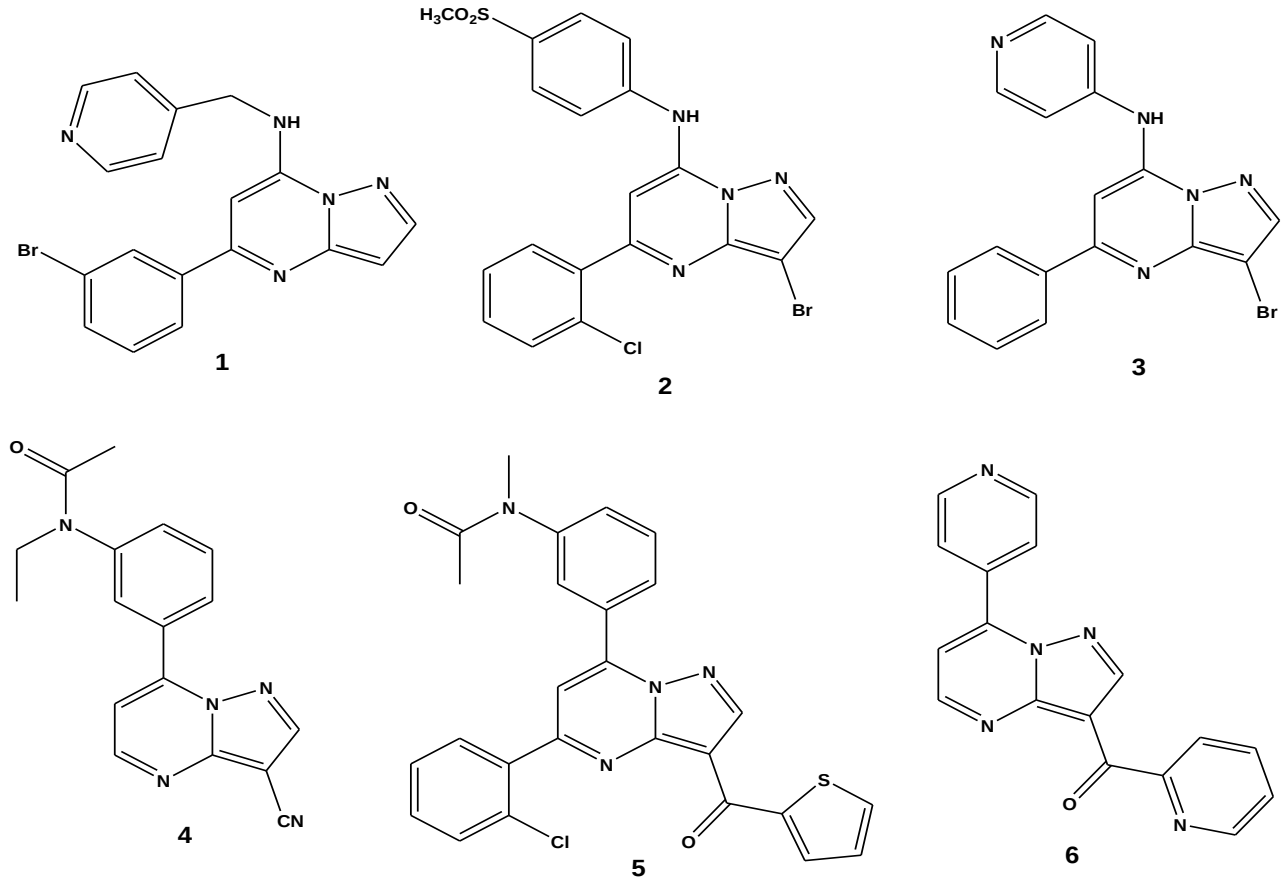
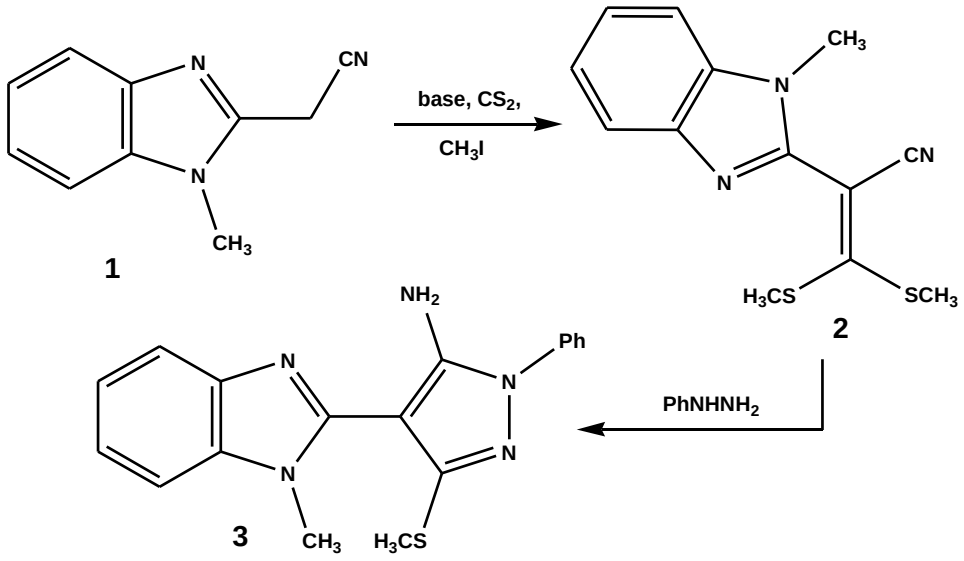


Figure 1. 7-Substituted pyrazolo[1,5-a]pyrimidine suc has Zaleplon 4, Indiplon 5 and Ocinaplon 6



Scheme 1. Synthesis of 5-aminopyrazole derivative (3)

2. Chemistry

Treatment of 2-(1-methyl-1H-benzo[d]imidazol-2-yl)-3, 3-bis-(methylthio)acrylonitrile (2) with phenylhydrazine affords the target 4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-amine (3). The structure of (3) was esta-blished and confirmed as the reaction product on the basis of their elemental analysis and spectral data. The IR spectrum showed absorption band in the region 3285 cm-1 assignable for NH2, in addition to disappearance of nitrile function signal. Its 1H NMR spectrum revealed the presence of singlet signals at δ 2.62 ppm, δ 3.98 ppm and δ 5.72 ppm assignable to the SCH3, N-CH3 and NH2 protons, respectively. Its mass spectrum showed a molecular ion peak

at m/z = 335 corresponding to a molecular formula C18H17N5S. (Scheme 1).

Treatment of4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-amine (3) with (3,5-dimethy-1H-pyrazol-1-yl)-3-oxopropanenitrile as cyanoacetylation reagent in dry toluene afforded 2-cyano-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acetamide (4). The structure of (4) was established on the basis of spectral data. The IR spectrum revealed absorption band at 3215 cm^{-1} for the NH group, sharp band at 2218 cm^{-1} for the cyano function and strong band at 1658 cm^{-1} for carbonyl group. Its 1H NMR spectrum revealed the presence of singlet signals at δ 4.12 ppm and δ 10.65 ppm assignable to the methylene and NH protons, respectively. Its mass spectrum showed a molecular ion peak at m/z = 402 corresponding to a molecular formula C21H18N6OS. The reactivity of 2-cyano-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl) acetamide (4) to give pyrazole, pyrimidinethione pyrazolopyrimidine and pyridopyrimidine derivatives was investigated.

Treatment of2-cyano-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl) acetamide (4) with DMF-DMA (5) in refluxing toluene afforded the corresponding2-cyano-3-(dimethylamino)-N-(4-(1-methyl-1H-benzo[d]-imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acrylamide (6). The struct-ure of the enaminonitrile (6) has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 3240 cm-1 due to the NH function, 2198 cm^{-1} due to the conjugated cyano function, 1663 cm^{-1} due to the amidic carbonyl function. The 1H NMR spectrum exhibited two sharp singlet signals at δ 3.21 ppm and δ 3.35 ppm assignable to N,N-dimethylamino protons, anther singlet signal at δ 8.09 ppm specific for methane proton and broad signal at δ 11.47 ppm due to NH proton. The mass spectrum showed a molecular ion peak at m/z = 457, corresponding to molecular formula C24H23N7OS. (scheme 2).

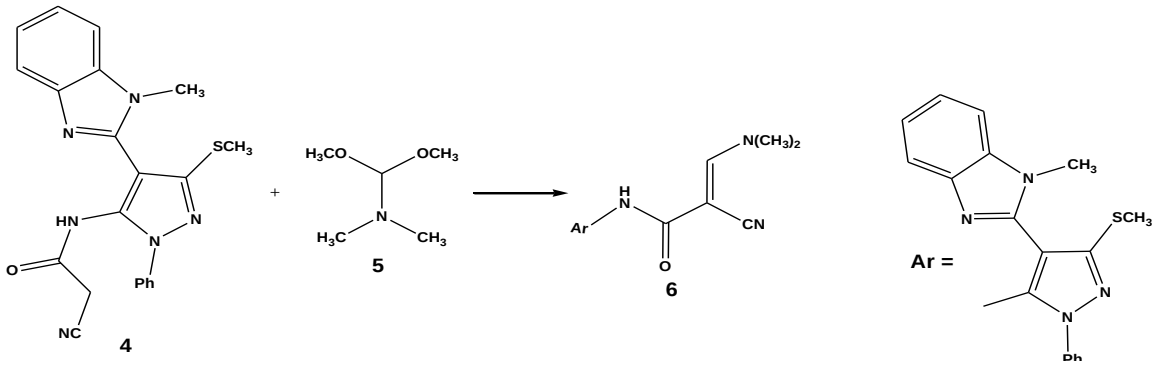
The behavior of the enaminonitrile (6) toward some N-nucleophiles to attain polyfunctionally substituted azoles, azines and related fused systems linked to pyrazole moiety through a carboxamide linkage of potential pharmaceutical interest, has been investigated.

Treatment of (6) with hydrazine hydrate at room temperature afforded 2-cyano-3-hydrazinyl-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acrylamide (7). The structure of acyclic hydrazine derivative (7) has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 3410 cm^{-1}, 3280 cm^{-1}, 3218 cm^{-1}, 3180 cm^{-1} due to the NH2 and NH functions, 2193 cm^{-1} due to cyano function, 1671 cm^{-1} due to the amidic carbonyl function. The 1H NMR spectrum exhibited four singlet signals at δ 5.04 ppm, δ7.78 ppm, δ 8.85 ppm and δ 10.25 ppm assignable to NH2, olefinic CH, 2NH protons, respectively. The mass spectrum showed a molecular ion peak at m/z = 444, corresponding to molecular formula C22H20N8OS. (scheme 3).

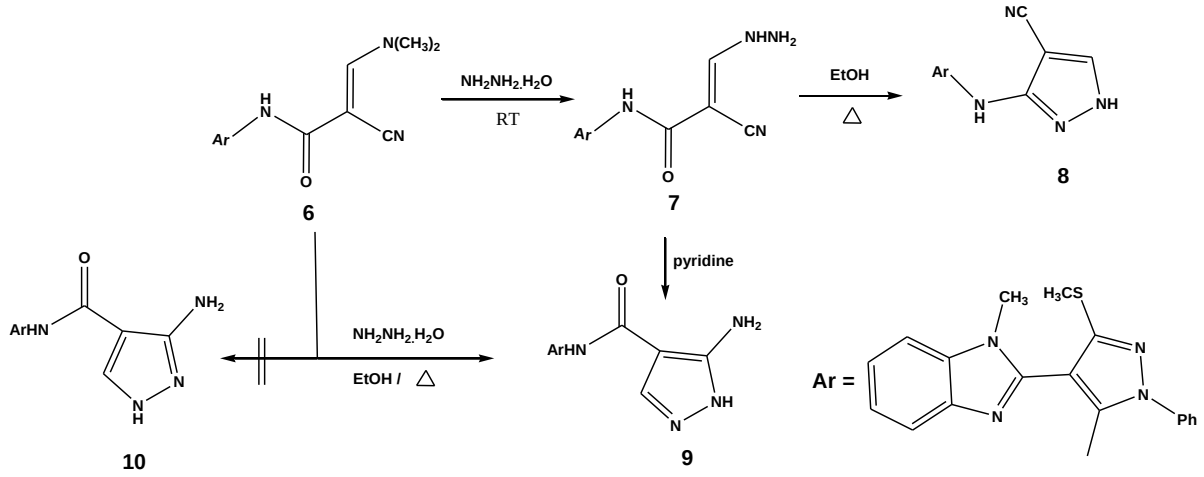
Refluxing of the acrylamide derivative (7) with stirring in ethanol gave the cyanopyrazole (8). The structure of the later has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 3270 cm^{-1}, 3164 cm^{-1} due to the (2NH) functions, 2228 cm-1 due to cyano function. The 1H NMR spectrum of (8) exhibited three singlet signals at δ 8.34 ppm, δ 13.04 ppm and δ 9.61 ppm assignable to 2NH and pyrazole-CH protons, respectively. The mass spectrum showed a molecular ion peak at m/z = 426, corresponding to molecular formula C22H18N8S. (scheme 3).

When the acrylamide (7) refluxed in pyridine solution, cyclization gradually took place via addition of amino of hydrazine to the cyano function afforded 5-aminopyrazole derivative (9) which achieved as a sole product. The structure of (9) has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 3430 cm^{-1}, 3354 cm^{-1} due to NH2 function, 3275 cm^{-1}, 3129 cm^{-1} due to the NH function, 1659 cm^{-1} due to the amidic carbonyl function. Inspection of 1H NMR spectrum enabled establishing structure (9) for this pyrazole derivative since the pyrazole H-3 appeared as a singlet signal at δ 8.19 ppm. We could not trace in the 1H NMR spectrum any signals for the tautomeric 3-amino-pyrazole (10) as this could reveal pyrazole-H5 as a doublet. The mass spectrum showed a molecular ion peak at m/z = 444, corresponding to molecular formula C22H20N8OS. (scheme 3).

The structure of 5-aminopyrazole derivative (9) was further confirmed by its alternate synthesis via stirring at 50-60℃ of 2-cyano-3-(dimethylamino)-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acryl-amide (6) with hydrazine hydrate which afforded product identical in all respects (mp, mixed mp, TLC and spectral data IR, 1H NMR and MS) with those of 5-aminopyrazole derivative (9) (scheme 3).



Scheme 2. Synthesis of acrylamide derivative (6)

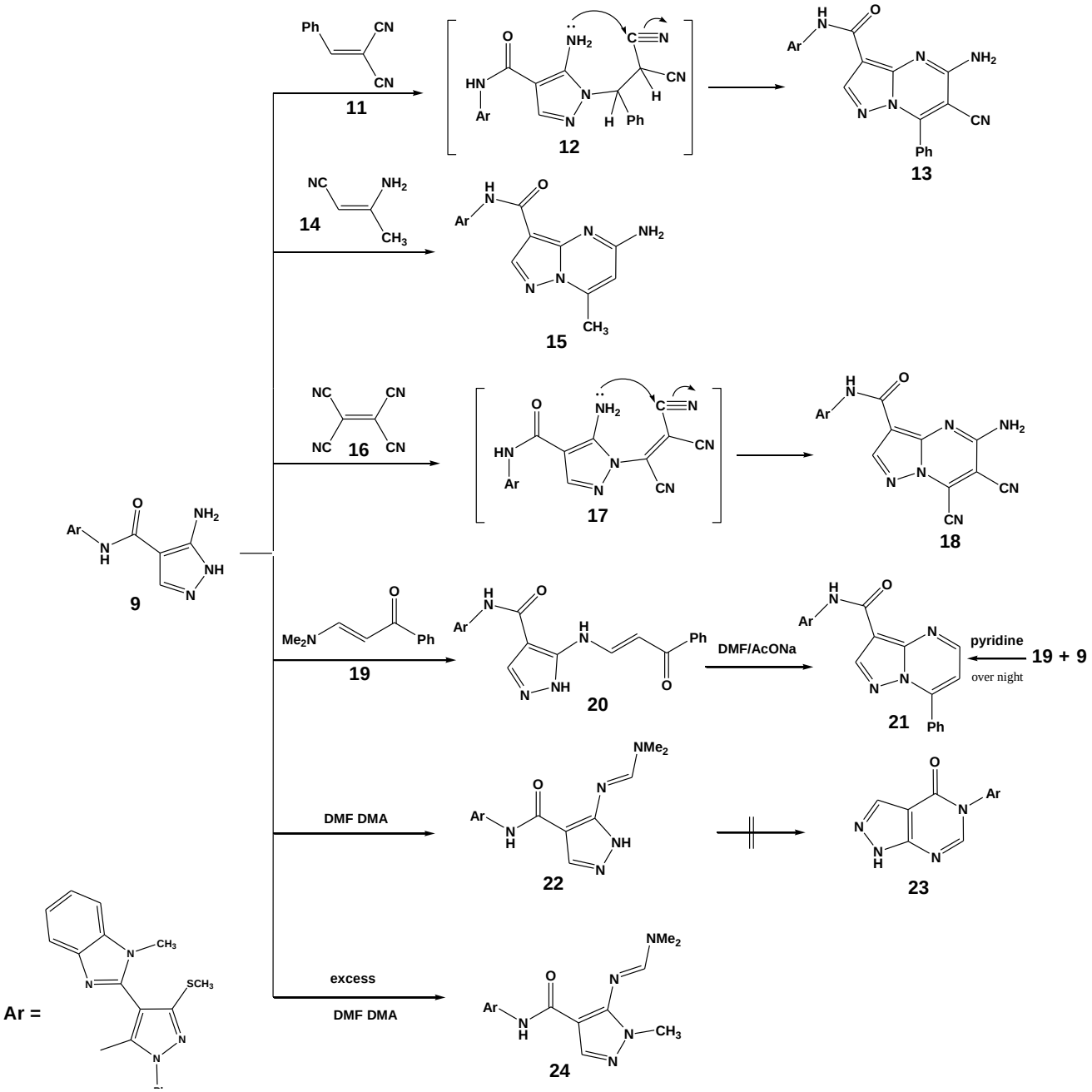


Scheme 3. synthesis of pyrazole derivatives (8) and (9)

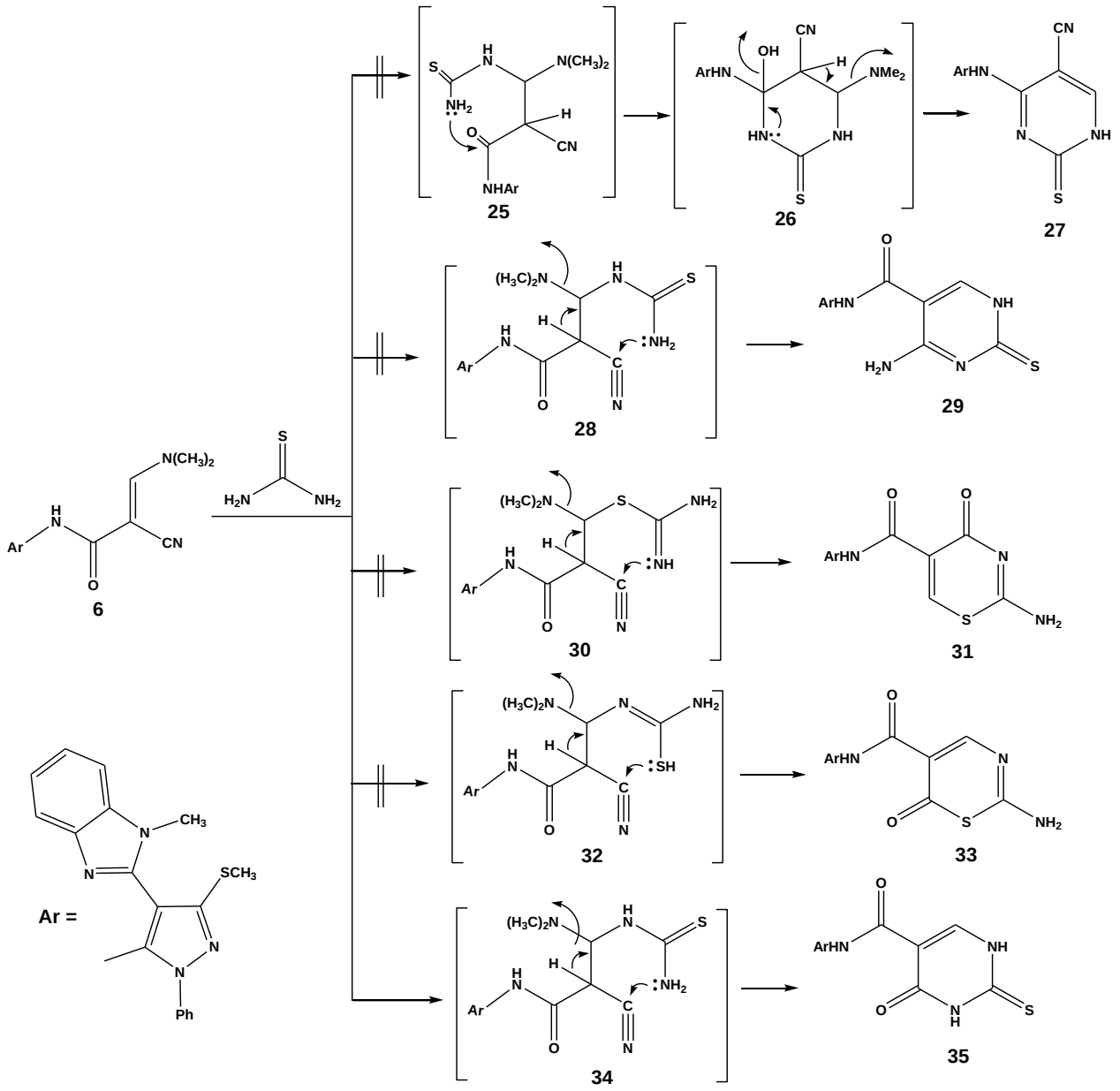
The reactivity of 5-amino-N-(4-(1-methyl-1H-benzo[d] imidazol-2-yl)-3-(methyl-thio)-1-phenyl-1H-pyrazol-5-yl)-1 H-pyrazole-4-carboxamide (9) toward some electrophilic reagents was investigated. Cyclization of (9) to the corresponding pyrazolo[1,5-a]pyrimidine derivatives (13) was achieved upon refluxing (9) with benzylidenemalononit rile (11) in ethanol containing few drops of piperidine as a basic catalyst. The structure of (13) was established by examining spectral and elemental analysis. The IR spectrum displayed absorption bands at 3450 cm^{-1}, 3338 cm^{-1}, 3250cm-1 due to the (NH and NH2) functions, 2203 cm^{-1} due to cyano function and 1665 cm^{-1} due to the amidic carbonyl. The 1H NMR spectrum of (13) exhibited two singlet signals at δ 3.92 ppm and δ 10.19 ppm assignable to NH2 and NH, respectively. The mass spectrum showed a molecular ion peak at m/z = 596, corresponding to molecular formula C32H24N10OS. The formation of (13) is assumed to proceed via initial Michael addition of the endocyclic NH in (9) to the double bond in benzylidene malononitrile to yield the non-isolable intermediate (12) followed by intramolecular cyclization and aromatization by loss hydrogen molecule to afford (13). When compound (9) was treated with 3-aminocrotononitrile (14) in glacial acetic acid, the corresponding pyrazolopyrimidine derivative (15) was obtained. The formation of (15) is assumed to proceed via condensation of the endocyclic NH in (9) with (14) followed by intramolecular cyclization afforded (15).

Reaction of (9) with tetracyanoethylene (16) in refluxing dioxane in the presence of catalytic amount of piperidine afforded the 5-aminopyrazolo[1,5-a]pyrimidine derivative (18). The molecular structure of compound (18) was confirmed on the basis of its elemental and spectral data. Its IR spectrum showed the characteristic absorption bands at 3411 cm^{-1}, 3318 cm^{-1}, 3252 cm^{-1} for (NH and NH2), 2203 cm^{-1} for CN group and 1648 cm^{-1} for C=O. The mass spectrum showed a molecular ion peak at m/z = 545, corresponding to molecular formula C27H19N11OS. Formation of pyrazolopyrimidine (18) take place as depicted in (scheme 4), via an initial Michael addition of the endocyclic NH in (9) to yield the non-isolable intermediate (17) followed by intramolecular cyclization to afford the corresponding (18).

Pyrazole (9) reacted smoothly with enaminones (19) to yield the acyclic product (20) that underwent cyclization to generate (21) upon refluxing in DMF/AcONa. It should be noted that the pyrazolo[1,5-a]pyrimidine (21) could be prepared directly from (9) and (19) in refluxing pyridine. Attempts to synthesis pyrazolo[3,4-d]-pyrimidine (23) by the reaction of (9) with DMF-DMA failed and only the amidines (22) were formed which did not cyclize to generate the corresponding (23). All analysis of compounds (21, 22, 24) are consistent with the proposed structures.



Scheme 4. synthesis of pyrazolopyrimidine derivatives 13, 15, 18 and 21



Scheme 5. synthesis of thioxopyrimidine (35)

The site selectivity in cycloaddition of some nitrogen ambident nucleophiles with enaminonitrile (6) was also investigate, Thus, reaction of (6) with thiourea in refluxing ethanol containing catalytic amount of piperidine afforded a single product for which five isomeric cycloadducts (27),(29),(31),(33) and (35) seemed possible. However, the pyrimidinethione (35) was assigned for the reaction product on its analysis. The IR spectrum lacked an absorption band due to a CN function and showed bands at 3386, 3161, 1673, 1635 and 1276cm^{-1} characteristic to 3NH, two amidic CO and CS functions., respectively. The 1H NMR spectrum exhibited no signal due to NH2 protons which was attributed to either structures (29), (31) or (33) and displayed doublet signal at δ 8.24ppm assignable to pyrimidine-H6 proton, three broad singlet signals at δ 9.01ppm, δ 11.07ppm and δ 11.73ppm, specific for three NH protons, in addition to an aromatic multiplet in the region δ 7.21-7.93ppm.

Also, reaction between enaminonitrile (6) and 6-amino-2-thioxo-(1H)-pyrimidine-4-one (36) in ethanol containing catalytic amount of piperidine afforded a single product (as examined by TLC) for which three isomeric cycloadducts (38), (40) and (41) seemed possible. However, the pyrido[2,3-d]pyrimidine derivative (41) was assigned for the reaction product on the basis of its elemental and spectral data. The IR spectrum lacked an absorption band due to a nitrile function and reaveled absorption bands at 3465 cm^{-1}, 3242 cm-1, 3216 cm^{-1} assigned to (NH and NH2), 1675 cm^{-1}, 1635 cm-1 characteristic to 2C=O functions., respectively. The 1H NMR spectrum exhibited singlet signal at δ 4.88 ppm due to NH2 protons which was attributed to (41) which is consistent isomeric structure (41) and three broad singlet signals at δ 10.91 ppm, δ 12.43 ppm and δ 13.05 ppm,

specific for three NH protons, in addition to an aromatic multiplet in the region δ 7.21-7.83 ppm. In addition, according to literature the reaction of hetercyclic amines to the double bond of the enaminonitrile occurs with concurrent elimination of dimethylamine rather than condensation of water molecule[45-57] but in our studying herein elimination of dimethylamine rather than addition on cyano group followed by aromatization. On the basis of these finding, structure of (38 and 40) was discarded and the product isolated from the studied reaction was assigned structure (41).

3. Experimental

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures, unless otherwise stated. All chemical were purchased from Aldrich or Across and used without purification. Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The 1H NMR spectra were determined in DMSO-d6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70Ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University. (3, 5-Dimethy-1H-pyrazol-1-yl)-3-oxopropanenitrile was prepared according to the reported literature[58].

4-(1-Methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-amine (3) was prepared according to the reported literature [59].

2).2-Cyano-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acetamide (4).

A solution of 4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-amine (3) (0.01 mol) in dry toluene (30 ml) was added to solution of with (3,5-dimethy-1H-pyrazol-1-yl)-3-oxopropanenitrile (0.01 mol) in dry toluene (30 ml). The reaction mixture was refluxed for about 1h. After evaporation of the solvent, the solid product was collected by filtration and recrystallised from dry DMF to afford (83%, yield) of (4), mp 293-295 ℃; IR υmax / cm-1 (KBr) 3215, 3172 (NH), 2218 (CN), 1658 (CO), 1630 (C=N); 1H NMR (DMSO-d6) δ 2.68 (s, 3H, SCH3), 3.91 (s, 3H, NCH3), 4.12 (s, 2H, CH2), 7.51-8.01 (m, 9H, Ar-H), 10.65 (s, 1H, NH); m/z 402 (M+, 13.75). Anal. Calcd. For C21H18N6OS (402.47): C, 62.67; H, 4.51; N, 20.88; S, 7.97%. Found: C, 62.63; H, 4.49; N, 20.78; S, 7.94%.

3).2-Cyano-3-(dimethylamino)-N-(4-(1-methyl-1H-benzo[d]-imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acrylamide (6).

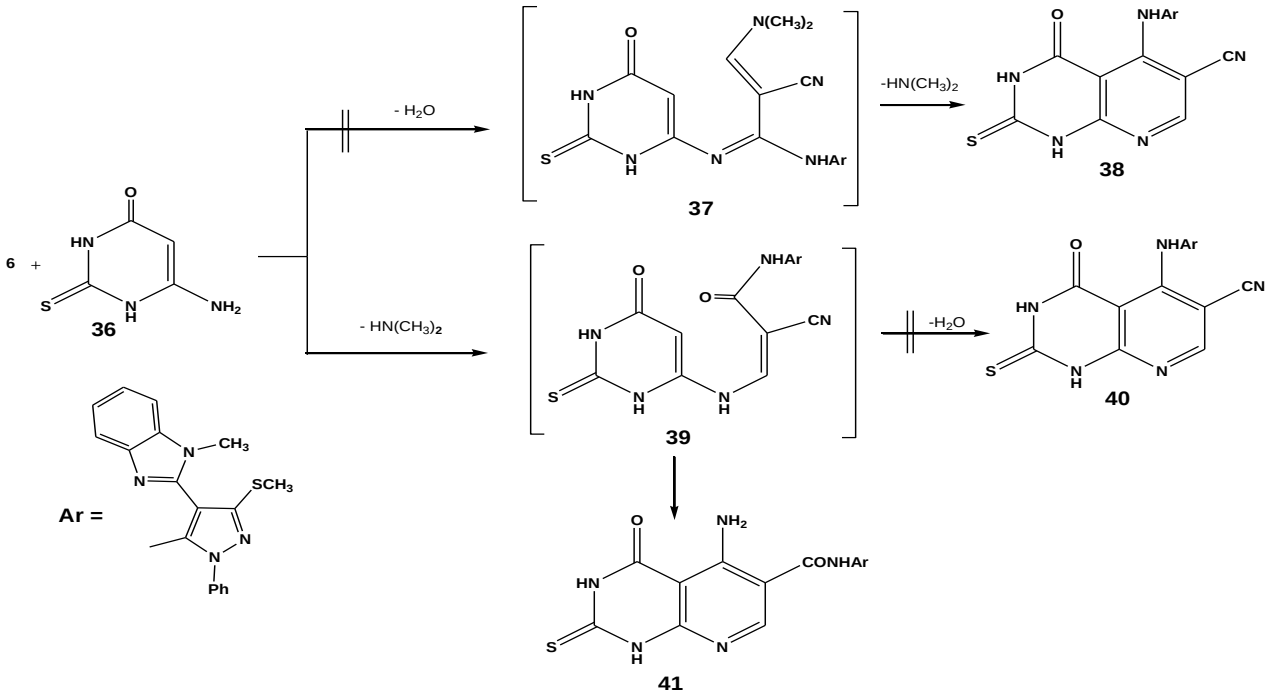
A mixture of 2-cyano-N-(4-(1-methyl-1H-benzo[d] imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acetamide (4) (10 mmol) and DMF/DMA (5) (1.2g, 10mmol) in. dry toluene.(25 ml) was stirred at room temperature for 6h. The separated solid product formed on standing at room temperature. The pale orange precipitate product was filtered off, washed with diethyl ether, dried and recrystallized from toluene to give (84%, yield) of (6), mp 256°C; IR υmax / cm-1 (KBr) 3240 (NH), 2198 (CN), 1663 (amidic C=O), 1630 (C=N); 1H NMR (DMSO-d6) δ 2.67 (s, 3H, SCH3), 3.21 (s, 3H, NCH3), 3.35 (s, 3H, NCH3), 3.94 (s, 3H, NCH3), 7.25-7.93 (m, 9H, Ar-H), 8.09 (s, 1H, CH=), 11.47 (s, br, 1H, NH); m/z 457 (M+, 29.12). Anal. Calcd. For C24H23N7OS (457.55): C, 63.00; H, 5.07; N, 21.43; S, 7.01%. Found: C, 62.96; H, 5.02; N, 21.40; S, 7.10%.

4).2-Cyano-3-hydrazinyl-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)acrylamide (7).

A solution of the enaminonitrile (6) (10mmol) and hydrazine hydrate (80%. 0.65 ml) in ethanol (40 ml) were stirred at reflux for 30 minutes, then cooled to room temperature. The solid product was separated by filtration, washed with ethanol, and recrystallized from dioxan as white crystals to give (69%, yield) of (7), mp 231°C; IR υmax / cm-1 (KBr) 3410, 3280, 3218, 3180 (NH2 and 2NH), 2193 (CN), 1671 (amidic C=O), 1628 (C=N); 1H NMR (DMSO-d6) δ 2.69 (s, 3H, SCH3), 3.92 (s, 3H, NCH3), 5.04 (s, br, 2H, NH2), 7.78 (s, 1H, CH=), 7.21-7.97 (m, 9H, Ar-H), 8.85 (s, br, 1H, NH), 10.25 (s, br, 1H, NH); m/z 445 (M++1, 28.6), 444 (M+, 100). Anal. Calcd. For C22H20N8OS (444.51): C, 59.44; H, 4.54; N, 25.21; S, 7.21%. Found: C, 59.42; H, 4.56; N, 25.18; S, 7.17%.

5).3-(4,5-Dihydro-4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-ylamino)-1H-pyrazole-4-carbonitrile (8).

A mixture of the enaminonitrile (7) (10 mmol) and hydrazine hydrate (80%. 0.65 ml) in ethanol (40 ml) stirred at reflux for 4h., then concentrated in vacuo to one third of its volume, cooled to room temperature, poured onto ice/water. The solid product which formed was collected by filtration, washed with water several times and recrystallized from dioxan to give (76%, yield) of (8), mp 261-263°C; IR υmax / cm-1 (KBr) 3270, 3164 (2NH), 2228 (CN), 1632 (C=N); 1H NMR (DMSO-d6) δ 2.70 (s, 3H, SCH3), 3.95 (s, 3H, NCH3), 7.31-8.02 (m, 8H, Ar-H), 8.34 (s, br, 1H, NH), 9.61 (s, 1H, pyrazole H-5), 13.04 (s, br, 1H, NH), 10.25 (s, br, 1H, NH); m/z 427 (M++1, 12.7), 426 (M+, 37). Anal. Calcd. For C22H18N8S (426.5): C, 61.95; H, 4.25; N, 26.27; S, 7.52%. Found: C, 61.86; H, 4.23; N, 26.26; S, 7.54%.



Scheme 6. synthesis of 2-thioxo pyrido[2,3-d] pyrimidin-4-one derivative (41)

6).5-Amino-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-1H-pyrazole-4-carboxamide (9).

Method (A). Compound (6) (10 mmol) in ethanol (25ml) was treated with hydrazine hydrate (80%. 0.65 ml) stirred at 50-60℃ for 5h. Cooling to room temperature afforded a precipitate which was separated by filtration, washed with ethanol and recrystallized from DMF/EtOH (2:1) as pale yellow crystals.

Method (B). A solution of (7) (10 mmol) in pyridine (20 ml) was stirred at reflux for 5h., and concentrated in vacuo gave a residue which was triturated with methanol to afford the solid product which was separated by filtration, washed with methanol and recrystallized from DMF/EtOH (2:1) as pale yellow crystals to give (71%, yield) of (9), mp 253℃; IR υmax / cm^{-1} (KBr) 3430, 3354, 3275, 3129 (NH2 and 2NH), 1659 (amidic C=O), 1628 (C=N); 1H NMR (DMSO-d6) δ 2.69 (s, 3H, SCH3), 3.94 (s, 3H, NCH3), 5.93 (s, br, 2H, NH2), 7.19-7.92 (m, 9H, Ar-H), 8.19 (s, 1H, pyrazole H-3), 10.15 (s, 1H, NH), 11.89 (s, br, 1H, NH); m/z 444 (M+, 43). Anal. Calcd. For C22H20N8OS (444.51): C, 59.44; H, 4.54; N, 25.21; S, 7.21%. Found: C, 59.43; H, 4.51; N, 25.23; S, 7.20%.

7).5-Amino-6-cyano-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-7-phenyl pyrazolo[1,5-a]pyrimidine-3-carboxamide (13).

A mixture of (9) (10 mmol), benzylidenemalononitrile (11) (10 mmol) and piperidine (0.5 ml) in ethanol (30 ml) was heated under reflux for 5h., the solid product which was produced on heating was collected by filtration and recrystallized from dimethylformamide as pale brown to give (58%, yield) of (13), mp 281-282°C; IR υmax / cm^{-1} (KBr) 3450, 3338, 3250 (NH2 and NH), 2203 (CN), 1665 (amidic C=O), 1628 (C=N); 1H NMR (DMSO-d6) δ 2.68 (s, 3H, SCH3), 3.96 (s, 3H, NCH3), 3.92 (s, 2H, NH2; D2O-exchangeable), 7.20-7.98 (m, 14H, Ar-H), 8.61 (s, 1H, pyrazole H-3), 10.19 (s, 1H, NH; D2O-exchangeable); m/z 596 (M+, 12.43). Anal. Calcd. For C32H24N10OS (596.66): C, 64.42; H, 4.05; N, 23.48; S, 5.37%. Found: C, 64.45; H, 3.98; N, 23.46; S, 5.36%.

8).5-Amino-7-methyl-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (15).

A mixture of compound (9) (10 mmol), β-aminocrotononitrile (14) (10 mmol) in glacial acetic acid (15 ml) was heated under reflux for 1h., then allowed to cool and poured onto water. The solid product was collected by filtration and recrystallized from dioxin to give (58%, yield) of (15), mp 273-275°C; IR υmax / cm^{-1} (KBr) 3450, 3330, 3300, 3248 (NH2 and NH), 1654 (amidic C=O), 1630 (C=N); 1H NMR (DMSO-d6) δ 2.51 (s, 3H, CH3), 2.69 (s, 3H, SCH3), 3.98 (s, 3H, NCH3), 6.98 (s, 2H, NH2; D2O-exchangeable), 6.17 (s, 1H, pyrimidine-H), 7.35-7.93 (m, 9H, Ar-H), 8.63 (s, 1H, pyrazole H-3), 10.60 (s, 1H, NH; D2O-exchangeable); m/z 509 (M+, 8.6). Anal. Calcd. For C26H23N9OS (509.59): C, 61.28; H, 4.55; N, 24.74; S, 6.29%. Found: C, 61.25; H, 4.54; N, 24.78; S, 6.24%.

9).5-Amino-6,7-dicyano-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (18).

A mixture of (9) (10 mmol), tetracyanoethylene (16) (10 mmol) and piperidine (0.5 ml) in dioxan (25 ml) was heated under reflux for 1h., the solid product which was produced on cooling was collected by filtration and recrystallized from acetic acid to give (66%, yield) of (18), mp > 300℃; IR υmax / cm-1 (KBr) 3411, 3318, 3252 (NH2 and NH), 2201,

2208 (2CN), 1648 (amidic C=O), 1631 (C=N); 1H NMR (DMSO-d6) δ 2.69 (s, 3H, SCH3), 3.97 (s, 3H, NCH3), 5.12 (s, 2H, NH2; D2O-exchangeable), 7.25-7.94 (m, 9H, Ar-H), 8.59 (s, 1H, pyrazole H-3), 10.23 (s, 1H, NH; D2O-exchangeable); m/z 545 (M+, 34.11). Anal. Calcd. For C27H19N11OS (545.58): C, 59.44; H, 3.51; N, 28.24; S, 5.88%. Found: C, 59.41; H, 3.52; N, 28.21; S, 5.91%.

10).5-(-3-Oxo-3-phenylprop-1-enylamino)-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-1H-pyrazole-4-carboxamide (20).

A mixture of (9) (10 mmol) and enaminone (19) (10 mmol) in pyridine (20 ml) were stirred at reflux for 5h., cooled to room temperature and poured onto ice/water acidified with hydrochloric acid, forming a solid that was collected by filtration, washed with water several times and recrystallized from dimethylformamide as yellow crystals to give (71%, yield) of (20), mp 291-293°C; IR υmax / cm-1 (KBr) 3330, 3178, 3142 (3NH), 1680, 1645 (2 CO), 1623 (C=N); 1H NMR (DMSO-d6) δ 2.68 (s, 3H, SCH3), 3.99 (s, 3H, NCH3), 6.21 (d, J = 8.0 Hz, 1H, prop-1-enylamino H-2), 7.32-7.98 (m, 15H, Ar-H and prop-1-enylamino H-1), 8.62 (s, 1H, pyrazole H-3), 10.57 (s, 1H, NH; D2O-exchangeable), 12.43 (d, 1H, NH) and 12.96 (s, 1H, NH); m/z 576 (M++1, 6.9), 575 (M+, 32.13). Anal. Calcd. For C31H26N8O2S (575.66): C, 64.79; H, 4.56; N, 19.50; S, 5.58%. Found: C, 64.76; H, 4.49; N, 19.46; S, 5.57%.

11).N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (21).

Refluxing of (20) (10 mmol) in DMF (20 ml) containing anhydrous sodium acetate (1g) for 6h. The reaction mixture was cooled to room temperature and poured onto ice. The aqueous solution was acidified with hydrochloric acid, forming a solid that was collected by filtration, washed with water several times and recrystallized from DMF as pale buff crystals to give (73%, yield) of (21), mp 275-277°C; IR υmax / cm-1 (KBr) 3283 (NH), 1692 (CO), 1625 (C=N); 1H NMR (DMSO-d6) δ 2.69 (s, 3H, SCH3), 3.97 (s, 3H, NCH3), 7.14 (d, 1H, pyrimidine H-6), 7.58-8.05 (m, 14H, Ar-H), 7.83 (d, 1H, pyrimidine H-5), 7.98 (s, 1H, pyrazole H-3), 10.64 (s, 1H, NH; D2O-exchangeable); m/z 557 (M++1, 3.9), 556 (M+, 25.5). Anal. Calcd. For C31H24N8OS (556.64): C, 66.89; H, 4.35; N, 20.13; S, 5.76%. Found: C, 66.86; H, 4.39; N, 20.10; S, 5.72%.

12).5-(Formamido)-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-1H-pyrazole-4-carboxamide (22). 5-(Formamido)-1-methyl-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-1H-pyrazole-4-carboxamide (24).

A mixture of (9) (5 mmol) and DMFDMA (5 mmol) in case of (22) or (11 mmol) in case of (24) in dimethylformamide (25 ml) was stirred at reflux for 5h., cooled to room temperature and poured onto ice/water. The formed crude solid was collected by filtration, washed with water several times and recrystallized from the appropriate solvent.

13).5-(Formamido)-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-1H-pyrazole-4-carboxamide (22).

Recrystallized from ethanol as yellow crystals to give (73%, yield) of (22), mp 231-232°C; IR υmax / cm^{-1} (KBr) 3422, 3220 (2NH), 1671 (CO); 1H NMR (DMSO-d6) δ 2.70 (s, 3H, SCH3), 3.08 (s, 3H, CH3), 3.13 (s, 3H, CH3) 3.99 (s, 3H, NCH3), 7.45-8.11 (m, 9H, Ar-H), 8.31 (s, 1H, imino CH), 9.24 (s, 1H, pyrazole H-3), 10.72 (s, 1H, NH; D2O-exchangeable); 12.68 (s, 1H, NH; D2O-exchangeable); m/z 499 (M+, 22.3). Anal. Calcd. For C25H25N9OS (499.59): C, 60.10; H, 5.04; N, 25.23; S, 6.42%. Found: C, 60.15; H, 4.99; N, 25.22; S, 6.39%.

14).5-(Formamido)-1-methyl-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-1H-pyrazole-4-carboxamide (24).

Recrystallized from dimethylformamide/ethanol as yellow crystals to give (81%, yield) of (24), mp 212-213°C; IR υmax / cm^{-1} (KBr) 3154 (NH), 1689 (CO); 1H NMR (DMSO-d6) δ 2.70 (s, 3H, SCH3), 3.12 (s, 3H, CH3), 3.16 (s, 3H, CH3), 3.86 (s, 3H, CH3), 3.98 (s, 3H, NCH3), 7.42-7.93 (m, 9H, Ar-H), 8.28 (s, 1H, imino CH), 9.35 (s, 1H, pyrazole H-3), 10.68 (s, 1H, NH; D2O-exchangeable); m/z 513 (M+, 31.54). Anal. Calcd. For C26H27N9OS (513.62): C, 60.80; H, 5.30; N, 24.54; S, 6.24%. Found: C, 60.76; H, 5.32; N, 24.52; S, 6.28%.

15).1,2,3,4-Tetrahydro-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-4-oxo-2-thioxopyrimidine-5-carboxamide (35).

A mixture of enaminonitrile (6) (10 mmol) and thiourea (10 mmol) in mixture of dimethylformamide and ethanol (1:1) (25 ml) containing a catalytic amount of piperidine (0.1 ml) was refluxed for 6-8h (TLC control) and then left overnight at room temperature. The solid product so formed was filtered off, washed with ethanol and dried well and recrystallized from dimethylformamide as a pale yellow powder (81%, yield) of (35), mp 212-213°C; IR υmax / cm-1 (KBr) 3386- 3161 (3NH), 1673, 1635 (2 amidic C=O), 1276 (C=S); 1H NMR (DMSO-d6) δ 2.71 (s, 3H, SCH3), 3.98 (s, 3H, NCH3), 7.23-7.98 (m, 9H, Ar-H), 8.24 (d, J = 6.8 Hz, 1H, pyrimidine H-6), 9.01 (s, br, 1H, NH, D2O-exchangeable), 11.07 (s, br, 1H, NH, D2O-exchangeable), 11.73 (s, br, 1H, NH; D2O-exchangeable); m/z 489 (M+, 30.2). Anal. Calcd. For C23H19N7O2S2 (489.57): C, 56.43; H, 3.91; N, 20.30; S, 13.10%. Found: C, 56.40; H, 3.87; N, 20.27; S, 13.12%.

16).5-Amino-1,2,3,4-tetrahydro-N-(4-(1-methyl-1H-benzo[d]imidazol-2-yl)-3-(methylthio)-1-phenyl-1H-pyrazol-5-yl)-4-oxo-2-thioxopyrido[2,3-d]pyrimidine-6-carboxamide (41).

A mixture of enaminonitrile (6) (10 mmol) and 6-amino-2-thioxopyrimidine-4(1H)-one (36) (10 mmol) in dioxan (25 ml) containing a catalytic amount of piperidine (0.1 ml) was refluxed for 6-8h (TLC control) and then cooled to room temperature and poured onto ice/water. The formed crude solid was collected by filtration, washed with ethanol several times and recrystallized from DMF as a yellow crystals (61%, yield) of (41), mp > 300°C; IR υmax / cm-1 (KBr) 3465, 3242, 3216 (NH and NH2), 1675, 1635 (2

amidic C=O), 1275 (C=S); 1H NMR (DMSO-d6) δ 2.71 (s, 3H, SCH3), 3.98 (s, 3H, NCH3), 4.88 (s, br, 2H, NH2, D2O-exchangeable), 7.23-7.98(m, 9H, Ar-H), 8.45 (s, 1H, pyridine H-2), 10.91 (s, br, 1H, NH, D2O-exchangeable), 12.43 (s, br, 1H, NH, D2O-exchangeable), 13.05 (s, br, 1H, NH; D2O-exchangeable); m/z 555 (M+, 9.75). Anal. Calcd. For C26H21N9O2S2 (555.63): C, 56.20; H, 3.81; N, 22.69; S, 11.54%. Found: C, 56.11; H, 3.79; N, 22.74; S, 11.53%.

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