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SYNTHESIS AND REACTIVITY OF CYANOMETHYL THIAZOLYL KETONE: A FACILE SYNTHESIS OF SOME NEW AZOLES, CHROMENE, PYRIDINE, THIOPHENE, PYRAZOLO[3,4-*b*]PYRIDINE AND PYRIMIDO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES

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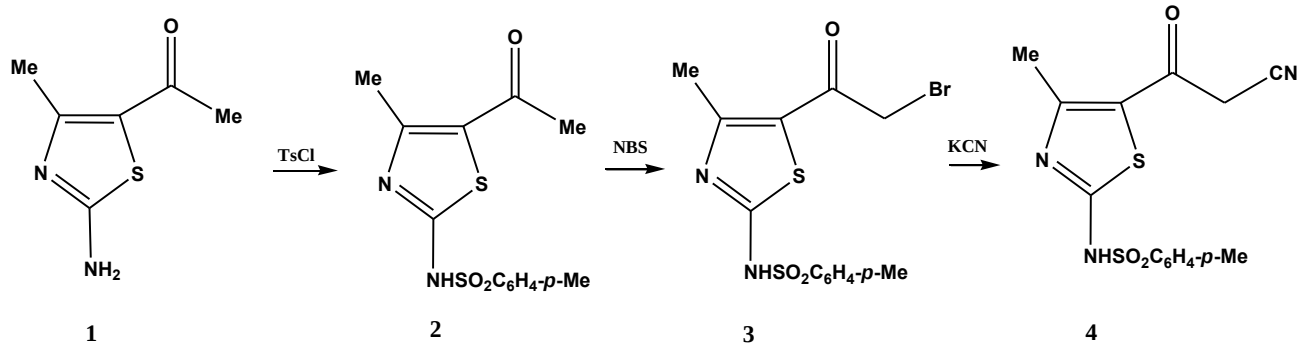
Abstract – Several new heterocyclic compounds such as chromene, pyrazole, isoxazole, dihydropyridine, thiazole, thiophene, pyrazolopyridine and pyrimidobenzimidazole derivatives have been synthesized by the reactions of the versatile multifunctional unreported 3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile with several nitrogen binucleophiles. A one-pot three component reaction of an aldehyde, the 3-oxopropanenitrile derivative, and electron-rich heterocyclic amines has been decribed.

Thiazoles[1-8] and their derivatives are important building blocks for the synthesis of many heterocyclic system of great value from biological point of view. Also, the pharamacological and biological activities of pyrazolo[3,4-*b*]pyridine,[9-13] and pyrimido[1,2-*a*]benzimidazole,[14-18] derivatives are well documented. In view of these observations and in continuation of our current interest in the synthesis of polysubstituted heterocycles for biological evaluations,[19-29] we described herein a facile synthesis of novel thiazole derivatives with expected biological activity starting from 2-benzylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (**5a**). Previously we have reported the synthesis of 3-(2-amino-4-methylthiazol-5-yl)-3-oxopropanenitrile and its reactivity towards some α,β-unsaturated nitriles and nitrogen nucleophiles.[24] As part of our ongoing research program directed toward the synthesis of several heterocyclic ring systems bearing different type and number of substituents, we report here on the synthesis of several heterocyclic ring systems bearing pyrazole, pyridine, benzimidazole and thiophene moieties starting from the versatile hitherto unreported 3-(4-methyl-2-(tosylamino)-thiazol-5-yl)-3-oxopropanenitrile (**4**). Herein we described, a facile synthesis of pyrazolo[3,4-*b*]pyridine derivative and pyrimido[1,2-*a*]benzimidazole derivative by three-component one-pot reaction of benzaldehyde, 3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (**4**), and electron-rich amino heterocycles in dimehylformamide under mild conditions.

1-(4-Methyl-2-(tosylamino)thiazol-5-yl)ethanone (**2**) was synthesized in good yield by the reaction of 1-(2-amino-4-methylthiazol-5-yl)ethanone (**1**) with 4-methylbenzene-1-sulfonyl chloride in refluxing

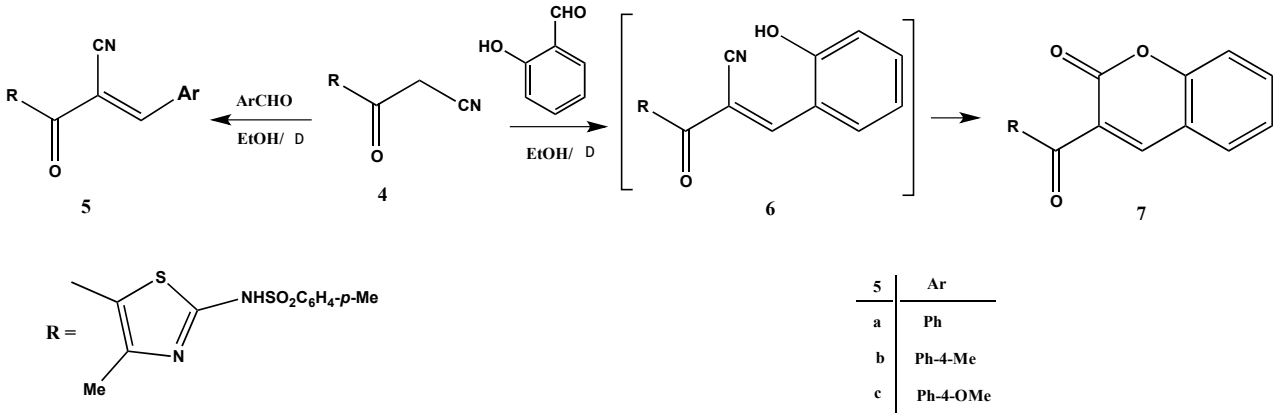
pyridine. The assignment of structure **2** was supported by elemental analysis and spectral data. The IR spectrum showed the absorption bands at 1644 and 3162 cm^{-1} assignable to carbonyl and NH group, respectively. Its H^1 NMR spectrum exhibited a signal at δ 13.09 ppm assignable to NH proton. Its mass spectrum showed the molecular ion peak at *m/z* 310 (M^+, 21) which is in agreement with the expected molecular formula ($C_{13}H_{14}N_2S_2O_3$). Reaction of **2** with *N*-bromosuccinimide in chloroform solution afforded the corresponding 2-bromo-1-(4-methyl-2-(tosylamino)thiazol-5-yl)ethanone (**3**). The assignment of structure **3** was supported by elemental analysis and spectral data. The ^1H NMR spectrum of **3** exhibited a signal at δ 4.35 ppm assignable to methylene protons. Its mass spectrum showed the molecular ion peak at *m/z* 487 (M^+, 26) which is in agreement with the expected molecular formula ($C_{13}H_{13}N_2S_2BrO_3$). Reaction of **3** with ethanolic potassium cyanide solution gave the desired 3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (**4**). The structure of **4** was confirmed on the basis of analytical and spectral data. The IR spectrum showed the absorption band at 2232 cm^{-1} assignable to cyano group. Its H^1 NMR spectrum exhibited a signal at δ 4.79 ppm assignable to methylene protons. The mass spectrum showed the molecular ion peak at *m/z* 335 (M^+, 19) corresponding to the molecular formula ($C_{14}H_{13}N_3S_2O_3$) (Scheme 1).



Scheme 1

Arylacetonitriles are highly reactive multifunctional synthetic intermediates which undergo a wide range of condensation and cyclization reactions.[26] The active methylene moiety in the thiazolylacetonitrile **4** condensed easily with aromatic aldehydes in ethanol in the presence of a catalytic amount of piperidine as a basic catalyst to afford the corresponding Knoevenagel product 2-arylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile **5a-c** (Scheme 2). The structures of the isolated products (**5a-c**) were assigned as the *E*-isomer based on the previous reported.[30] For example, the IR of 2-benzylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (**5a**) showed a strong carbonyl and nitrile bands at 1717 and 2191 cm^{-1}, respectively. Its ^1H NMR spectrum revealed signals at δ 12.83, 8.25 and 7.31-7.71 ppm due to NH, methine and aromatic protons, respectively. Its mass spectrum showed a molecular ion peak at *m/z* 423 (M^+, 15) corresponding to a molecular formula ($C_{21}H_{17}N_3O_3S_2$). Treatment of compound **4** with salicylaldehyde under basic conditions afforded (4-methyl-2-(tosylamino)thiazol-5-yl)(2*H*-2-oxochromen-3-yl)methanone (**7**). The structure of **7** was confirmed on the

basis of analytical and spectral data. The IR spectrum revealed the absence of cyano group absorption band and the presence of new absorption band at 1711 cm^{-1} assignable to lactone carbonyl group. Its ^1H NMR spectrum exhibited singlet signal at δ 8.49 ppm assignable to *H-4* of coumarin ring. The mass spectrum showed the molecular ion peak at *m/z* 440 (M^+, 7) corresponding to the molecular formula ($C_{21}H_{16}N_2O_5S_2$) (Scheme 2). The formation of chromene derivative **7** could be explained by the reaction sequence as in Scheme 2. Firstly, a Knoevenagel condensation afforded the non-isolable intermediate followed by intramolecular cyclization to coumarin derivatives **7** (Scheme 2).

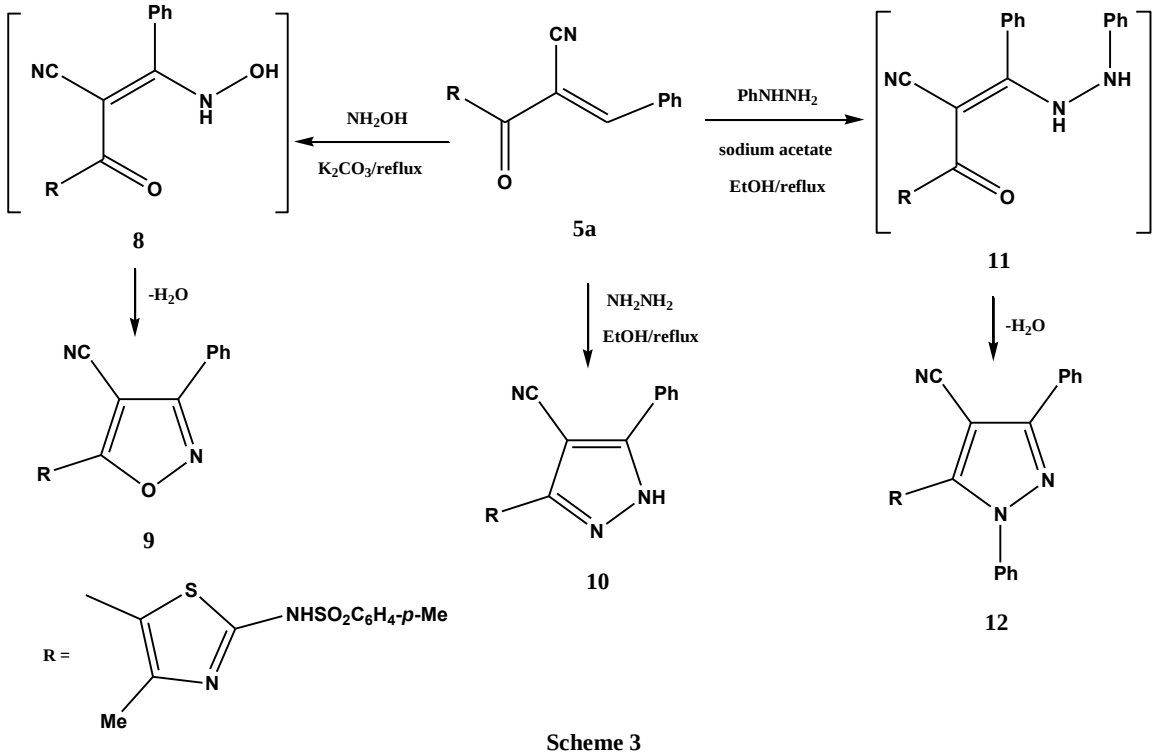


Scheme 2

Subsequent addition of nitrogen containing reagents that possess two nucleophile centers provides a means to convert 2-benzylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (**5a**) to functionalized heterocycles. Thus, treatment of 2-benzylidene-3-oxopropanenitrile derivative **5a** with hydroxylamine hydrochloride in refluxing ethanol in the presence of sodium acetate afforded a white solid product of 5-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-phenylisoxazole-4-carbonitrile (**9**) that is not readily soluble in any solvent (Scheme 3). The isoxazole derivative **9** is assumed to be formed via formation of non-isolable intermediate **8** which underwent condensation and intramolecular cyclization followed by oxidation that is driven by the formation of an aromatic heterocycle to afford the isoxazole derivative **9**. The structure of **9** was confirmed on the basis of analytical and spectral data. The IR spectrum revealed the absence of carbonyl group absorption band and showed band at 2209 cm^{-1} corresponding to nitrile function. Its ^1H NMR spectrum revealed signals at δ 12.98 and 7.13-7.82 ppm due to NH and phenyl protons, respectively. The mass spectrum showed the molecular ion peak at *m/z* 436 (M^+, 10) corresponding to the molecular formula ($C_{21}H_{16}N_4O_3S_2$).

Also, compound **5a** reacts with hydrazine, in refluxing ethanol, to afford 3-(4-methyl-2-(tosylamino)-thiazol-5-yl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**10**) as shown in Scheme 3. The formation of pyrazole derivative **10** was assumed to proceed by a sequence of 1,4-addition, cyclization with loss of water, followed by late stage oxidation that is driven by the formation of an aromatic heterocycle. The structure of **10** was confirmed on the basis of analytical and spectral data. The IR spectrum revealed the absence of carbonyl group absorption band and the presence of absorption band at 2192 cm^{-1} assignable to cyano

function. Its ^{1}H NMR spectrum exhibited two singlet signals at δ 13.3 and 11.54 ppm assignable to SO_2NH (*D_2O*-exchangeable) and NH-pyrazole, respectively. The mass spectrum showed the molecular ion peak at *m/z* 435 (M^+, 16) corresponding to the molecular formula ($C_{21}H_{17}N_5O_2S_2$). Also, 2-benzylidene-3-oxopropanenitrile derivative **5a** reacts with phenylhydrazine in refluxing ethanol in the presence of sodium acetate to afford the 5-(4-methyl-2-(tosylamino)thiazol-5-yl)-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile (**12**). The formation of pyrazole derivative **12** was assumed to proceed by initial 1,4-addition of phenylhydrazine, followed by rapid oxidation to provide firstly stable vinylogous amide-like structure (**11**) due to the steric hindrance of phenyl group, then the vinylogous amide-like structure **11** converted to pyrazole derivative **12** by loss of water. The structure of **12** was confirmed on the bases of their elemental analysis and spectral data (see experimental section) (Scheme 3).



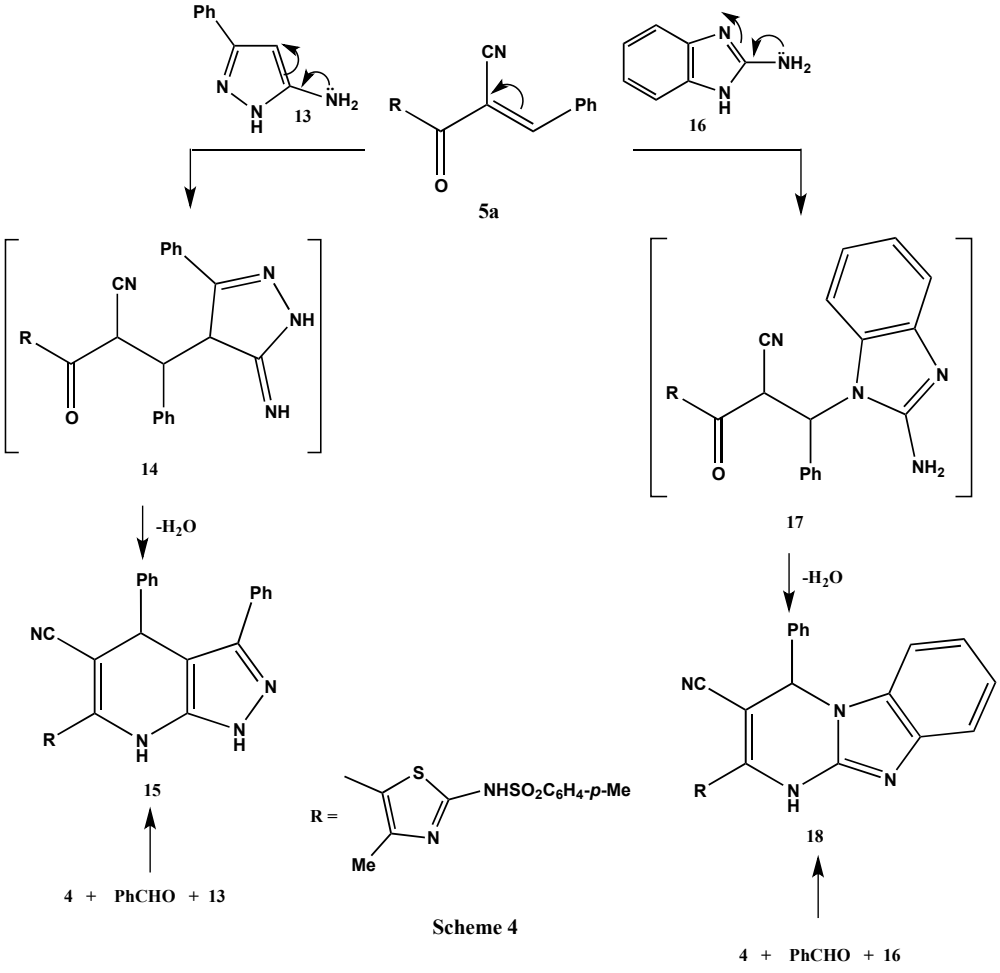
Scheme 3

The behaviors of 2-benzylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile **(5a)** towards electron-rich amino heterocycles were also investigated. Thus, treatment of **5a** with 5-amino-3-phenyl-(1*H*)-pyrazole (**13**), in refluxing ethanol in the presence of a catalytic amount of triethylamine as a basic catalyst, furnished a product identified as 4,7-dihydro-6-(4-methyl-2-(tosylamino)thiazol-5-yl)-3,4-diphenyl-(1*H*)-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**15**) (Scheme 4). The structure of **15** was confirmed on the basis of analytical and spectral data. Its ^{1}H NMR spectrum exhibited three *D_2O*-exchangeable singlet signals at δ 10.64, 12.63 and 12.98 ppm assignable to NH protons of pyridine, pyrazole, and sulfone, respectively. The mass spectrum showed the molecular ion peak at *m/z* 564 (M^+, 12) corresponding to the molecular formula ($C_{30}H_{24}N_6O_2S_2$).

Furthermore, compound **15** was prepared with high yield by three-component one-pot reaction of

benzaldehyde, 3-oxopropanenitrile **4**, and 5-amino-3-phenyl-(1*H*)-pyrazole (**13**) in DMF at room temperature. The formation of compound **15** procceded via Knoevenagel condensation reaction of benzaldehyde with 3-oxopropanenitrile **4** to give 2-benzylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile **(5a)**, followed by Michael addition of electron-rich amino pyrazole **13** to provide the non-isolable intermediate **14**, that underwent condensation and intramolecular cyclization to afford compound **15**.[31] The comparison between the yield of compound **15** in the two synthetic methods indicate that, the yield of **15** from method MCRs was higher compared to the other direct reaction of **5a** and **13** due to the solvent effect, where DMF in method B was considered as more aprotic solvent than ethanol in method A, so that DMF enhance Michael addition of electron-rich aminopyrazole **13** to provide the non-isolable intermediate **14**.

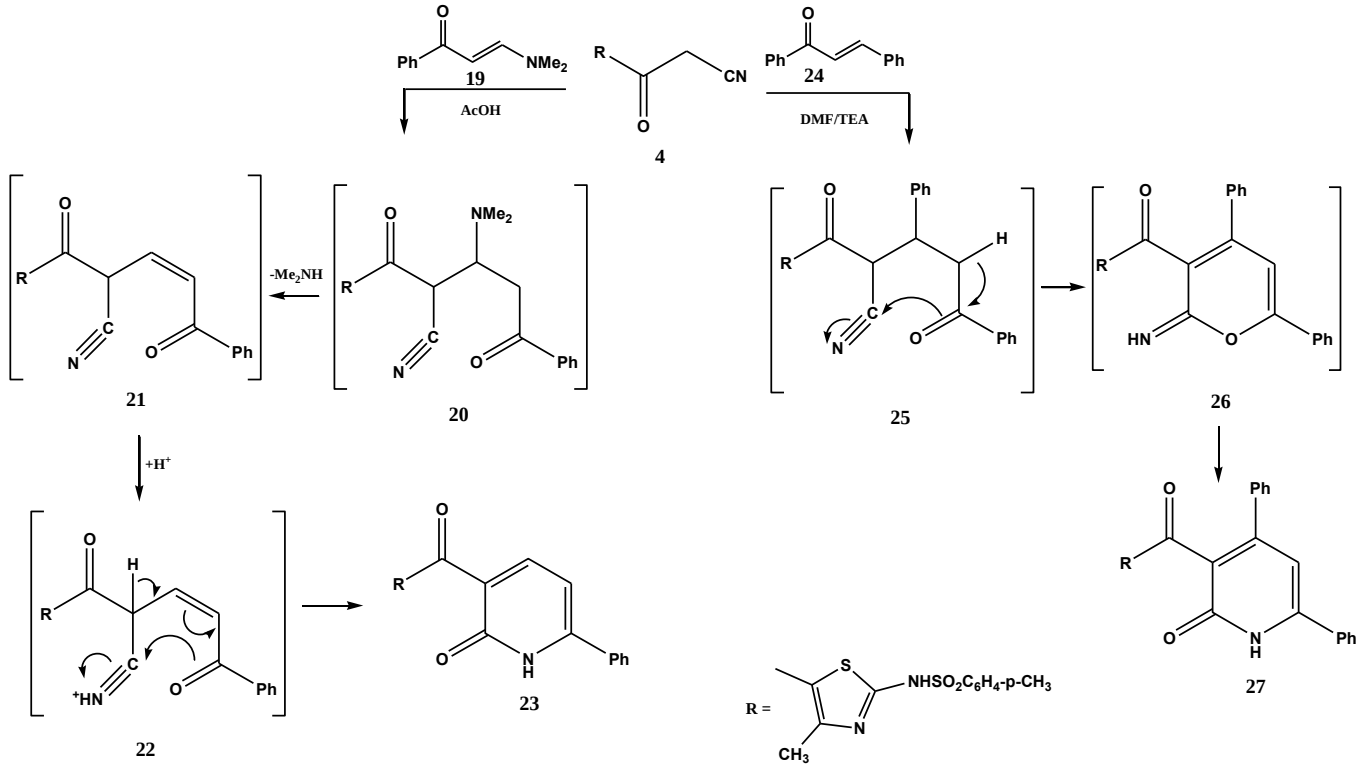
Three-component one-pot condensation of benzaldehyde, β-ketonitrile **4**, and 2-aminbenzimidazole (**16**), in (Biginelli and Biginelli like reactions,[32,33]) DMF at room temperature afforded 2-(4-methyl-2-(tosyl-amino)thiazol-5-yl)1,4-dihydro-4-phenylpyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**18**). The forma-tion of the product **18** proceeded via Knoevenagel condensation of benzaldehyde with **4** followed by Michael addition of 2-aminobenzimidazole **16** and subsequent intramolecular cyclization condensation (Scheme 4).



Scheme 4

The formation of **23** was assumed to proceed via Michael addition of the active methylene nitrile **4** to α,β-unsaturated ketone to yield the corresponding Michael adduct **20**, followed by the deamination reaction,

an intramolecular cyclization and the Dimroth rearrangement following by autoxidation. On the other hand, compound **23** was also formed according to the proposed mechanism as shown in Scheme 5.[34] In a similar manner, treatment of compound **4** with chalcone **24** in refluxing DMF containing a catalytic amount of triethylamine as a basic catalyst afforded the corresponding 4-methyl-*N*-(4-methyl-5-(2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonyl)thiazol-2-yl)benzenesulfonamide (**27**). The structure of **27** was confirmed on the basis of analytical and spectral data. Its IR spectrum revealed the absence of cyano absorption band. Its ^{1}H NMR spectrum exhibited singlet signal at δ 6.12 ppm assignable to *H-5* of pyridine ring. The mass spectrum showed the molecular ion peak at *m/z* 541 (M^+, 53) corresponding to the molecular formula ($C_{29}H_{23}N_3O_4S_2$).

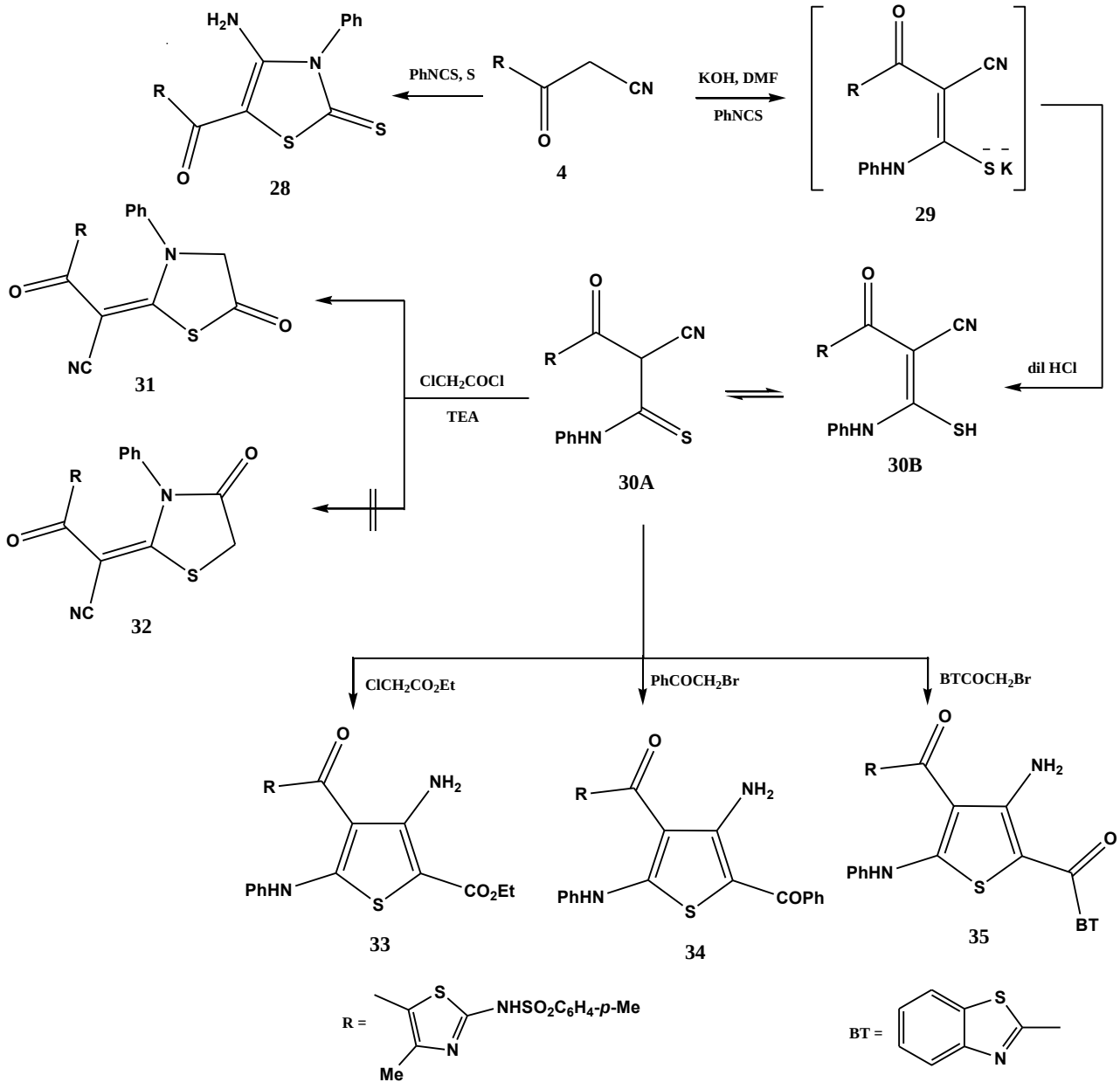


Scheme 5

Treatment of compound **4** with sulfur and phenyl isothiocyanates in refluxing DMF containing a catalytic amount of triethylamine as a basic catalyst afforded the corresponding *N*-(5-(4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbonyl)-4-methylthiazol-2-yl)-4-methylbenzenesulfonamide (**28**). The structure of **28** was confirmed on the basis of analytical and spectral data. Its IR spectrum showed absorption bands at 3425 and 3237 cm^{-1} assignable to NH_2 and NH. Its ^{1}H NMR spectrum exhibited singlet signal at δ 6.72 ppm assignable to NH_2 The mass spectrum showed the molecular ion peak at *m/z* 502 (M^+, 5) corresponding to the molecular formula ($C_{21}H_{18}N_4O_3S_4$).

Next, we turned out our attention to the reaction of **4** with phenyl isothiocyanate in DMF in the presence

of potassium hydroxide to afford the corresponding 2-cyano-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxo-*N*-phenylpropanethioamide (**30**) upon treatment with dilute hydrochloric acid (Scheme 6). The assignment of structure **30** was supported by elemental analysis and spectral data. The IR spectrum revealed the absorption bands at 3386, 2252, 1686 and 1273 cm^{-1} assignable to NH, CN, CO and C=S groups, respectively. Its ^1H NMR spectrum exhibited singlet signal at δ 4.32 ppm assignable to aliphatic CH proton which means that compound **30** is solely present in **30A** form instead of its tautomer **30B**. The mass spectrum showed the molecular ion peak at *m/z* 470 (m^+, 12) corresponding to the molecular formula ($C_{21}H_{18}N_4O_3S_3$).



Scheme 6

Compound **30A** is a versatile multifunctional reagent and its reactivity towards active methylene compounds is studied. When compound **30A** was treated with an equimolar amount of chloroacetyl

chloride in DMF and TEA, 3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxo-2-(5-oxo-3-phenylthiazolidin-2-ylidene)propanenitrile (**31**) or its isomer 3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxo-2-(4-oxo-3-phenylthiazolidin-2-ylidene)propanenitrile (**32**) was obtained. The thiazole **32** is excluded based on the spectral data. The ^{1}H NMR spectrum revealed the presence of singlet signal at δ 4.28 ppm assignable to *H-4* of thiazole ring[34] not for *H-5* which should appear at approximately δ 3-4 ppm. Also, the presence of thiazole methylene between carbonyl and *N*-phenyl in compound **31** lead to appearance methylene protons at more downfield than those in compound **32** which have methylene between carbonyl and sulfur. Finally, the thiocarbamyl derivative **30A** reacted with each of ethyl chloroacetate, phenacyl bromide and 1-(benzothiazol-2-yl)-2-bromoethanone in refluxing DMF containing a catalytic amount of triethylamine to afford single product, which in each case, was identified as the aminothiophene derivatives (**33-35**), respectively, based on the elemental analysis and spectral data of isolated products (see experimental). For example, the IR spectrum of (4-amino-5-(benzothiazol-2-carbonyl)-2-(phenylamino)thiophen-3-yl)(4-methyl-2-(tosylamino)thiazol-5-yl)methanone (**34**) revealed the absence of cyano absorption band. Its ^{1}H NMR spectrum revealed the presence of three singlet signals *D$_2$O*-exchangeable at δ 5.96, 10.62 and 13.2 ppm assignable to NH_2, and 2NH, respectively. The mass spectrum showed the molecular ion peak at *m/z* 645 (M^+, 18) corresponding to the molecular formula ($C_{30}H_{23}N_5O_4S_3$).

In the present work we describe the syntheses of 3-oxopropanenitrile derivatives and its reactivity towards nitrogen nucleophiles such as hydrazine, phenylhydrazine and hydroxylamine hydrochloride to give isoxazole, pyrazole and 1,3-diphenyl-1*H*-pyrazole derivatives, respectively. We have described also an efficient synthesis of one-pot three component reaction of aldehyde, 3-oxo-propanenitrile and electron rich heterocyclic amines such as 5-aminopyrazole and aminobenzimidazole to afford pyrazolopyridine and pyrimidobenzimidazole derivatives, respectively.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded KBr disk on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in DMSO-*d$_6$* 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. 1-(2-amino-4-methylthiazol-5-yl)ethanone **1**[35] and 1-(benzothiazol-2-yl)-2-bromoethanone[36] were prepared according to the reported literature.

1-(4-Methyl-2-(tosylamino)thiazol-5-yl)ethanone (2).

To a solution of 1-(2-amino-4-methylthiazol-5-yl)ethanone (10 mmol) **1** (10 mmol) in pyridine (30 mL) 4-methylbenzene-1-sulfonyl chloride (10 mmol) was added. The reaction mixture was heated under

reflux for 2 h, and then, the reaction mixture was allowed to cool and poured on ice cold water containing hydrochloric acid. The precipitate was filtered off and crystallized from dioxane to give compound **2**; buff powder; yield (70.5%); mp 135-137 °C. IR (cm^{-1}): υ 3162 (NH), 1644 (CO). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 7.35 (d, *J* = 7.8 *Hz*, 2H, Ar-H), 7.71 (d, *J* = 7.8 *Hz*, 2H, Ar-H), 13.09 (s, 1H, NH, *D_2O*-exchangeable); MS *m/z* (%): 310 (M^+, 21). Anal. Calcd for $C_{13}H_{14}N_2S_2O_3$: C, 50.30; H, 4.55; N, 9.03. Found: C, 49.98; H, 4.51; N, 8.99%.

2-Bromo-1-(4-methyl-2-(tosylamino)thiazol-5-yl)ethanone (3).

A mixture of **2** (10 mmol) and *N*-bromosuccinimide (10 mmol) in $CHCl_3$ (30 mL) was refluxed for 5 h, then allowed to cool. The precipitate was filtered off, washed with water, dried, and finally recrystallized from EtOH to afford compound **3**; yellow powder; yield (62.3%); mp 227-228 °C. IR (cm^{-1}): υ 3157 (NH), 1646 (CO). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 7.36 (d, *J* = 8.4 *Hz*, 2H, Ar-H), 7.72 (d, *J* = 8.4 *Hz*, 2H, Ar-H), 13.05 (s, 1H, NH, *D_2O*-exchangeable); MS *m/z* (%): 387 (M^+, 26). Anal. Calcd for $C_{13}H_{13}BrN_2S_2O_3$: C, 40.11; H, 3.37; N, 7.20. Found: C, 39.97; H, 3.33; N, 6.99%.

3-(4-Methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (4).

To a solution of **3** (10 mmol) in absolute EtOH (50 mL), was added a solution of potassium cyanide (10 mmol in 10 mL water) with stirring. The reaction mixture was heated on a boiling water bath. The reaction mixture was left at room temperature overnight, with stirring, then dilutrd with water. The solid that precipitated was filtered off, washed with water, dried, and finally recrystallized from DMF to afford compound **4**; yellow powder; yield (46.5%); mp 165-167 °C. IR (cm^{-1}): υ 3172 (NH), 2232 (CN), 1648 (CO). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 7.31 (d, *J* = 8.4 *Hz*, 2H, Ar-H), 7.71 (d, *J* = 8.4 *Hz*, 2H, Ar-H), 12.99 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 195.8, 182.3, 158.1, 143.6, 137.2, 130.4 (2C), 128.1 (2C), 116, 112.6, 29.2, 24.7, 12.8; MS *m/z* (%): 335 (M^+, 19). Anal. Calcd for $C_{14}H_{13}N_3O_3S_2$: C, 50.13; H, 3.91; N, 12.53. Found: C, 49.96; H, 3.66; N, 12.49%.

Synthesis of 2-arylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (5a-c).

To a solution of compound **4** (10 mmol) in absolute EtOH (50 mL) containing few drops of piperidine, the appropriate aldehyde (10 mmol) was added. The reaction mixture was heated under reflux for 5 h, and then, the reaction mixture was allowed to cool. The precipitate that formed was filtered off and recrystallized from the appropriate solvent to afford the corresponding 2-arylidene-3-oxopropanenitrile derivatives (**5a-c**).

(*E*) 2-Benzylidene-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (5a).

Yield (44%); pale yellow powder (from EtOH); mp 210-211 °C. IR (cm^{-1}): υ 3215 (NH), 2191 (CN), 1717 (CO). ^{1}H NMR: δ (ppm): 2.36 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.31-7.71 (m, 9H, Ar-H), 8.25 (s, 1H,

C=H), 12.83 (s, 1H, NH, *D*$_2$*O*-exchangeable); ^{13}C NMR δ (ppm): 188.7, 182.7, 165.9, 157.9, 149.2, 141.8, 136.4, 135.1, 130.1 (2C), 126.3 (2C), 128.6 (2C), 128.2, 127.7 (2C), 110.6, 116.4, 25.3, 13.7; MS *m/z* (%): 423 (M^+, 15). Anal. Calcd for $C_{21}H_{17}N_3O_3S_2$: C, 59.56; H, 4.05; N, 9.92. Found: C, 59.52; H, 4.02; N, 9.88%.

(*E*) 2-(4-Methylbenzylidene)-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (5b).

Yield (38.7%); pale brown powder (from DMF); mp 197-198 °C. IR (cm^{-1}): υ 3196 (NH), 2205 (CN), 1709 (CO). ^{1}H NMR δ (ppm): 2.35 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.89-7.43 (m, 8H, Ar-H), 8.32 (s, 1H, C=H), 12.92 (s, 1H, NH, *D*$_2$*O*-exchangeable); MS *m/z* (%): 437 (M^+, 20). Anal. Calcd for $C_{22}H_{19}N_3O_3S_2$: C, 60.39; H, 4.38; N, 9.60. Found: C, 60.35; H, 4.35; N, 9.54%.

(*E*) 2-(4-Methoxylbenzylidene)-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile (5c).

Yield (29.4%); brown powder (from dioxane); mp 221-223 °C. IR (cm^{-1}): υ 3211 (NH), 2189 (CN), 1703 (CO). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 6.86-7.39 (m, 8H, Ar-H), 8.31 (s, 1H, C=H), 12.96 (s, 1H, NH, *D*$_2$*O*-exchangeable); MS *m/z* (%): 453 (M^+, 26). Anal. Calcd for $C_{22}H_{19}N_3O_4S_2$: C, 58.26; H, 4.22; N, 9.27. Found: C, 58.21; H, 4.19; N, 9.25%.

(4-Methyl-2-(tosylamino)thiazol-5-yl)(2*H*-2-oxochromen-3-yl)methanone (7).

To a solution of compound **4** (10 mmol) in DMF (50 mL) containing triethylamine (0.5 mL), salicylaldehyde (10 mmol) was added. The reaction mixture was heated under reflux for 3 h, and then, the reaction mixture was allowed to cool. The precipitate that formed was filtered off and recrystallized from DMF to afford the corresponding compound **7**; yellowish brown; yield (41.8%); mp 169-171 °C. IR (cm^{-1}): υ 3188 (NH), 1711, 1674 (2CO). ^{1}H NMR δ (ppm): 2.35 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.21-7.85 (m, 8H, Ar-H), 8.49 (s, 1H, *H-4* coumarin), 12.87 (s, 1H, NH, *D*$_2$*O*-exchangeable); ^{13}C NMR δ (ppm): 187.3, 185.2, 161.6, 156.7, 151.2, 143.5, 140.6, 136.8, 130.2 (2C), 128.7, 128.2, 127.5 (2C), 127, 126.6, 122.3, 121.9, 111.6, 24.3, 12.3; MS *m/z* (%): 440 (M^+, 6). Anal. Calcd for $C_{21}H_{16}N_2S_2O_5$: C, 57.26; H, 3.66; N, 6.36. Found: C, 57.21; H, 3.63; N, 6.34%.

5-(4-Methyl-2-(tosylamino)thiazol-5-yl)-3-phenylisoxazole-4-carbonitrile (9).

To a mixture of **4** (10 mmol) and hydroxylamine hydrochloride (10 mmol) in EtOH (30 mL), was added anhydrous potassium carbonate (10 mmol). The resulting mixture was refluxed for 5-8 h, and allowed to cool to room temperature then diluted with water (50 mL). The solid product that formed was collected by filtration, washed with water, dried and finally recrystallized from DMF to afford the corresponding compound **9**; white powder; yield (69%); mp > 300 °C. IR (cm^{-1}): υ 3211 (NH), 2209 (CN). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.13-7.82 (m, 9H, Ar-H), 12.98 (s, 1H, NH, *D*$_2$*O*-exchangeable); ^{13}C NMR δ (ppm): 184.2, 166.8, 159.7, 153.9, 142.1, 136.4, 134.1, 129.8 (2C), 129.3 (2C), 128.7, 127.8 (2C), 127.4 (2C), 111.2, , 106.1, 24.3, 117, 11.3; MS *m/z* (%): 436 (M^+, 10). Anal.

Calcd for $C_{21}H_{16}N_4S_2O_3$: C, 57.78; H, 3.69; N, 12.84. Found: C, 57.72; H, 3.65; N, 12.82%.

3-(4-Methyl-2-(tosylamino)thiazol-5-yl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (10).

Hydrazine hydrate (80%, 2 mL) was added to a stirred solution of compound **5a** (10 mmol) in EtOH (20 mL). Stirring was continued overnight at room temperature and the obtained solid was filtered off, washed with cold water, dried and finally recrystallized from DMF to afforded compound **10**, pale yellow powder; yield (71%); mp 265-266 °C. IR (cm^{-1}): υ 3235, 3189 (NH), 2192 (CN). ^{1}H NMR δ (ppm): 2.34 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 7.14-7.81 (m, 9H, Ar-H), 11.54 (s, 1H, NH, *D_2O*-exchangeable), 13.3 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 187, 158.4, 150.3, 148.9, 143.4, 136.7, 133.9, 129.5 (2C), 129.1 (2C), 128.8, 127.6 (2C), 127.3 (2C), 110.5, 105.6, 24.6, 116.8, 10.9; MS *m/z* (%): 435 (M^+, 16). Anal. Calcd for $C_{21}H_{17}N_5S_2O_2$: C, 57.91; H, 3.93; N, 16.08. Found: C, 57.95; H, 3.96; N, 16.06%.

5-(4-Methyl-2-(tosylamino)thiazol-5-yl)-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile (12).

To a solution of compound **5a** (10 mmol) in EtOH (25 mL), were added phenylhydrazine (10 mmol) and sodium acetate (0.6 g). The reaction mixture was heated under reflux for 6 h, and then, the reaction mixture was allowed to cool and water was added (20 mL). The reaction mixture was stirred for 6 h, and then left overnight. The precipitate that formed was filtered off and recrystallized from DMF to afford the corresponding compound **12**; yellowish solid; yield (48.2%); mp 237-238 °C. IR (cm^{-1}): υ 3235, 3189 (NH), 2192 (CN). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.11-7.83 (m, 14H, Ar-H), 12.86 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 186.5, 157.4, 152.5, 149.9, 142.5, 140.4, 136.8, 135.2, 130 (2C), 129.4 (2C), 129.1 (2C), 128.9, 127.7 (2C), 127.3 (2C), 126.9, 121.3 (2C), 116.6, 112.8, 108.4, 25.6, 12.9; MS *m/z* (%): 411 (M^+, 4). Anal. Calcd for $C_{27}H_{21}N_5S_2O_2$: C, 63.38; H, 4.14; N, 13.69. Found: C, 63.35; H, 4.09; N, 13.64%.

4,7-Dihydro-6-(4-methyl-2-(tosylamino)thiazol-5-yl)-3,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (15) and 2-(4-Methyl-2-(tosylamino)thiazol-5-yl)1,4-dihydro-4-phenylpyrimido[1,2-*a*]benzimidazole-3-carbonitrile (18). (General Procedure):

Method A: To a mixture of **5a** (10 mmol) and 5-amino-3-phenyl-1*H*-pyrazole **13** or 2-amino-benzimidazole **16** (10 mmol) in EtOH (30 mL), was added and triethylamine (10 mmol). The resulting mixture was refluxed for 6 h, and allowed to cool to room temperature. The solid product that formed was collected by filtration, washed with EtOH, dried and finally recrystallized from the appropriate solvent to afford the corresponding compound **9** and **18**, respectively.

Method B: A mixture of benzaldehyde (10 mmol), **3**-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile 4 (10 mmol) and 5-amino-3-phenyl-1*H*-pyrazole **13** (10 mmol) or 2-amino-benzimidazole **16** (10 mmol) in dry DMF (20 mL) was stirred at room temperature for 48 h, to complete the reaction, then water was added (50 mL). The solid product that formed was collected by filtration, washed with water several times, dried and finally recrystallized from the appropriate solvent to afford

the corresponding compound **9** and **18**, respectively.

4,7-Dihydro-6-(4-methyl-2-(tosylamino)thiazol-5-yl)-3,4-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (15).

Yield [method A (41%), method B (79%)]; pale brown crystals (from DMF); mp 211-213 ^{o}C. IR (cm^{-1}): υ 3332, 3247 (2NH), 2195 (CN). ^{1}H NMR δ (ppm): 2.35 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 5.69 (s, 1H, CH), 7.21-7.59 (m, 14H, Ar-H), 10.64, 12.63, 12.98 (s, 3H, 3NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 181.9, 169.5, 160.2, 155.8, 145.9, 142.5, 139.8, 139.1, 136.7, 129.7 (2C), 129.5 (2C), 129.3 (2C), 129, 128.8 (2C), 127.9 (2C), 127.6 (2C), 125.8, 116.9, 112.7, 105.8, 90.2, 33.4, 25.8, 11.8; MS *m/z* (%): 564 (M^+, 12). Anal. Calcd for $C_{30}H_{24}N_6S_2O_2$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.77; H, 4.24; N, 14.86%.

2-(4-Methyl-2-(tosylamino)thiazol-5-yl)1,4-dihydro-4-phenylpyrimido[1,2-*a*]benzimidazole-3-carbonitrile (18).

Yield [method A (36%), method B (83%)]; pale yellow crystals (from dioxane); mp 239-240 ^{o}C. IR (cm^{-1}): υ 3335, 3214 (2NH), 2188 (CN). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.89 (s, 1H, CH), 7.05-7.84 (m, 13H, Ar-H), 9.2, 12.78 (s, 2H, 2NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 185.6, 164.9, 160.2, 156.6, 142.5, 139.1, 137.6, 136.8, 136, 130 (2C), 129.7 (2C), 128.7 (2C), 127.4 (2C), 126.2, 125.6 (2C), 118.8 (2C), 116.5, 109.2, 88.2, 51.3, 24.7, 12.1; MS *m/z* (%): 538 (M^+, 6). Anal. Calcd for $C_{28}H_{22}N_6S_2O_2$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.38; H, 4.09; N, 15.56%.

4-Methyl-*N*-(4-methyl-5-(2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonyl)thiazol-2-yl)benzene-sulfonamide (23).

A mixture of compound **4** (10 mmol) and (*E*)-3-(dimethylamino)-1-phenylprop-2-en-1-one **19** (10 mmol) was refluxed in glacial acetic acid (25 mL) in the presence of anhydrous sodium acetate (2 g) for 6 h. Then, the reaction mixture was allowed to cool to room temperature and poured onto ice cold water. The solid product that formed was collected by filtration, washed with water, dried and finally recrystallized from dioxane to afford the corresponding compound **23**; pale orange crystals; yield (71%); mp 286-288 ^{o}C. IR (cm^{-1}): υ 3385, 3282 (2NH), 1664, 1635 (2CO). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.10 (d, 1H, H-5$_{pyridine}$), 7.17-7.89 (m, 9H, Ar-H), 8.72 (d, 1H, H-4$_{pyridine}$), 10.87 (s, 1H, NH, *D_2O*-exchangeable), 13.02 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 182.6, 180.3, 162.3, 158, 157.1, 145.9, 142.8, 137.9, 136, 135.1, 129.2 (2C), 128.9 (2C), 128.5 (2C), 128, 127.2 (2C), 112.7, 103.6, 25.4, 12.4; MS *m/z* (%): 465 (M^+, 11). Anal. Calcd for $C_{23}H_{19}N_3S_2O_4$: C, 59.34; H, 4.11; N, 9.03. Found: C, 59.30; H, 4.07; N, 9.01%.

4-Methyl-*N*-(4-methyl-5-(2-oxo-4,6-diphenyl-1,2-dihydropyridine-3-carbonyl)thiazol-2-yl)benzene-sulfonamide (27).

To a solution of compound **4** (10 mmol) in DMF (25 mL), were added chalcone **24** (10 mmol) and triethylamine (0.5 mL). The reaction mixture was heated under reflux for 6 h, and then, the reaction mixture was allowed to cool and water was added (35 mL). The reaction mixture was stirred for 1 h, and then left overnight. The precipitate that formed was filtered off and recrystallized from DMF to afford the corresponding compound **27**; yellow powder; yield (70%); mp 2271-273 ^{o}C. IR (cm^{-1}): υ 3412, 3198 (2NH), 1686, 1633 (2CO). ^{1}H NMR δ (ppm): 2.34 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.12 (s, 1H, H-$5_{pyridine}$), 7.13-7.86 (m, 14H, Ar-H), 10.1 (s, 1H, NH, *D_2O*-exchangeable), 12.98 (s, 1H, NH, *D_2O*-exchangeable); MS *m/z* (%): 541 (M^+, 53). Anal. Calcd for $C_{29}H_{23}N_3S_2O_4$: C, 64.31; H, 4.28; N, 7.76. Found: C, 64.27; H, 4.25; N, 7.75%.

***N*-(5-(4-Amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbonyl)-4-methylthiazol-2-yl)-4-methyl-benzenesulfonamide (28).**

To a stirred solution of compound **4** (10 mmol) in DMF (25 mL), were added finely divided sulfur (10 mmol), triethylamine (1 mL) and phenyl isothiocyanate (10 mmol). The reaction mixture was heated under reflux for 6 h. The precipitate that formed was filtered off and recrystallized from EtOH to afford the corresponding compound **28**; brown crystals; yield (62%); mp 257-258 ^{o}C. IR (cm^{-1}): υ 3425, 3332 (NH_2), 3237 (NH), 1682 (CO), 1284 (C=S). ^{1}H NMR δ (ppm): 2.35 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 6.72 (s, 2H, NH_2), 7.11-7.83 (m, 9H, Ar-H), 12.83 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 189.3, 186.2, 183.7, 163.4, 156.9, 143.2, 136.7, 134.5, 129.8 (2C), 129 (2C), 127.4 (2C), 126.8 (2C), 125.1, 111, 84, 24.3, 11.9; MS *m/z* (%): 502 (M^+, 5). Anal. Calcd for $C_{21}H_{18}N_4S_4O_3$: C, 50.18; H, 3.61; N, 11.15. Found: C, 50.13; H, 3.56; N, 11.12%.

2-Cyano-3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxo-*N*-phenylpropanethioamide (30)

To a stirred solution of KOH (10 mmol) in DMF (20 mL), 3-(4-methyl-2-(tosylamino)thiazol-5-yl)-3-oxopropanenitrile **4** (10 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (10 mmol) was added to the resulting mixture. Stirring was continued for 6 h, then poured onto crushed ice containing HCl. The solid product so-formed was collected by filtration, washed with water, dried and finally recrystallized from EtOH/DMF to afford the corresponding compound **30**; brown powder; yield (83%); mp 201-203 ^{o}C. IR (cm^{-1}): υ 3386, 3189 (2NH), 2252 (CN), 1686 (CO), 1273 (C=S). ^{1}H NMR δ (ppm): 2.36 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.32 (s, 1H, CH), 7.13-7.79 (m, 9H, Ar-H), 10.69 (s, 1H, NH, *D_2O*-exchangeable), 12.87 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 197.3, 195.1, 182.3, 159.2, 137.7, 135.2, 131.1, 130 (2C), 129.3 (2C), 128.7, 127.1 (2C), 125.8, 117.4 (2C), 116.3, 59.2, 25.6, 11.9; MS *m/z* (%): 470 (M^+, 12). Anal. Calcd for $C_{21}H_{18}N_4S_3O_3$: C, 53.60; H, 3.86; N, 11.91. Found: C, 53.56; H, 3.85; N, 11.89%.

3-(4-Methyl-2-(tosylamino)thiazol-5-yl)-3-oxo-2-(5-oxo-3-phenylthiazolidin-2-ylidene)propane-nitrile (31).

A mixture of compound **30** (10 mmol) in DMF (20 mL), chloroacetyl chloride (10 mmol) and few drops of triethylamine was refluxed for 6 h, and then allowed to cool. The solid product so-formed was collected by filtration, dried and finally recrystallized from EtOH/DMF to afford the corresponding compound **31**; pale red crystals; yield (59%); mp 222-224 °C. IR (cm^{-1}): υ 3185 (NH), 2258 (CN), 1653, 1689 (2CO). ^{1}H NMR δ (ppm): 2.34 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.13-7.76 (m, 9H, Ar-H), 12.93 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 193.3, 188.2, 181.2, 164.1, 145.4, 142.6, 137.5, 130.2 (2C), 129.4 (2C), 129 (2C), 127.4 (2C), 118, 115.6, 112.7, 112 (2C), 73.4, 24.8, 12.3; MS *m/z* (%): 510 (M^+, 13). Anal. Calcd for $C_{23}H_{18}N_4S_3O_4$: C, 54.10; H, 3.55; N, 10.97. Found: C, 54.04; H, 3.52; N, 10.95%.

Synthesis of thiophene derivatives (33-35). (General Procedure).

To a solution of compound **30** (10 mmol) in DMF (20 mL), the appropriate α-halo carbonyl compounds such as ethyl chloroacetate, phenacyl bromide and 1-(benzothiazol-2-yl)-2-bromoethanone (10 mmol) and few drops of triethylamine were added. The reaction mixture was refluxed for 6 h, and then allowed to cool. The formed solid was collected by filtration, dried and finally recrystallized from the appropriate solvent to afford the corresponding thiophene derivatives **33-35**, respectively.

Ethyl 3-amino-4-(4-methyl-2-(tosylamino)thiazole-5-carbonyl)-5-(phenylamino)thiophene-2-carboxylate (33).

Yield (70%);pale orange powder (from DMF/H_2O); mp 293-294 °C. IR (cm^{-1}): υ 3439 (NH_2), 3337, 3285 (NH), 1726, 1652 (2CO). ^{1}H NMR δ (ppm): 1.21 (t, *J* = 7.2 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 4.36 (q, *J* = 7.2 Hz, 2H, OCH_2), 5.86 (s, 2H, NH_2), 7.11-7.81 (m, 9H, Ar-H), 10.68 (s, 1H, NH, *D_2O*-exchangeable), 13.02 (s, 1H, NH, *D_2O*-exchangeable); ^{13}C NMR δ (ppm): 184.8, 180, 168.3, 167.8, 156.9, 145.6, 144.5, 142.6, 137.3, 131.4, 130 (2C), 129.6 (2C), 127.8 (2C), 120.1, 119.2, 117 (2C), 111.7, 61.8, 24.6, 14.7, 11.9; MS *m/z* (%): 556 (M^+, 15). Anal. Calcd for $C_{25}H_{24}N_4O_5S_3$: C, 53.94; H, 4.35; N, 10.06. Found: C, 53.89; H, 4.30; N, 10.02%.

(4-Amino-5-benzoyl-2-(phenylamino)thiophen-3-yl)(4-methyl-2-(tosylamino)thiazol-5-yl)methanone (34).

Yield (62%); yellowish brown powder (from DMF); mp > 300 °C. IR (cm^{-1}): υ 3451 (NH_2), 3329, 3228 (NH), 1689, 1649 (2CO). ^{1}H NMR δ (ppm): 2.34 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 5.98 (s, 2H, NH_2), 7.13-7.82 (m, 14H, Ar-H), 10.56 (s, 1H, NH, *D_2O*-exchangeable), 13.05 (s, 1H, NH, *D_2O*-exchangeable); MS *m/z* (%): 588 (M^+, 13). Anal. Calcd for $C_{29}H_{24}N_4O_4S_3$: C, 59.16; H, 4.11; N, 9.52. Found: C, 59.12; H, 4.08; N, 9.48%.

(4-Amino-5-benzothiazol-2-carbonyl-2-(phenylamino)thiophen-3-yl)(4-methyl-2(tosylamino)thiazol-

5-yl)methanone (35).

Yield (62%); yellowish brown powder (from DMF); mp > 300 °C. IR (cm^{-1}): υ 3449 (NH_2), 3333, 3235 (NH), 1692, 1646 (2CO). ^1H NMR δ (ppm): 2.35 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 5.96 (s, 2H, NH_2), 7.33-8.23 (m, 13H, Ar-H), 10.62 (s, 1H, NH, *D_2O*-exchangeable), 13.2 (s, 1H, NH, *D_2O*-exchangeable); MS *m/z* (%): 645 (M^+, 18). Anal. Calcd for $C_{30}H_{23}N_5O_4S_3$: C, 55.79; H, 3.59; N, 10.84. Found: C, 55.71; H, 3.55; N, 10.80%.

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