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# Utility of Activated Nitriles in the Synthesis of Some New Heterocyclic Compounds

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**Abstract** New 4-(2-cyanoacetamido)benzoic acid (1) was utilized as key intermediate for the synthesis of some new thiazole, pyrazole, oxazole, pyrimidine, 1,3-dithiolane, thiophene, coumarin, oxazine and pyridazine derivatives. Newly synthesized compounds were characterized by elemental analyses and spectral data (IR, $^1$H NMR and mass spectra).

**Keywords** Cyanoacetamide, Cyanoketen *N,S*-acetal derivative, Enaminonitrile, 1,3-Dithiolane derivative

## 1. Introduction

Cyanoacetamides are highly reactive compounds. They are extensively utilized as reactants or reaction intermediates since the carbonyl and the cyano functions of these compounds are suitably situated to enable reactions with common bidentate reagents to form a variety of heterocyclic compounds. Moreover function, the active hydrogen on C-2 of these compounds can take part in a variety of condensation and substitution reactions.

The synthesis of cyanoacetamides may be carried out in several ways. The most economical method involves the treatment of substituted aryl or heteryl amines with alkyl cyanoacetates using different reaction conditions to yield cyanoacetamide derivatives. There are some methods used to prepare *N*- aryl or *N*-heterylcyanoacetamides [1, 2]. Cyanoacetyl pyrazole is a very handly and cheap cyanoacetylation reagent, which was the first time synthesized and introduced in common practice in late 1950 by Ried *et al* [3]. It was successfully applied for the synthesis of various *N*-alkyl and *N*-aryl cyanoacetamides.

Cyanoacetamides are polyfunctional compounds possessing both electrophilic and nucleophilic properties. Typical nucleophilic positions are NH and C-2 with reactivity order C-2 > NH. These chemical properties have been used to design different heterocyclic moiety with different ring size such as azirine, pyrrole, thiophene, pyrazole, imidazole, thiazole, thiadiazole, pyridine, pyrane, pyridazine, pyrimidine, and triazine. On the other hand, cyanoacetamide posses electrophilic positions especially at C-3, C-1 with reactivity order C-3 > C-1. So, cyanoacetamide can be useful for synthesis of three membered rings[4], five membred rings such as pyrrole derivative [5], pyrazole and their fused derivatives[6-8], imidazole[9], thiazole[10, 11], 1,3-dithiolane[12], thiadiazole and their derivatives[13, 14], thiophene [15, 16], also, six membered rings such as pyridine[17, 18], pyrane[19], pyradazine[20], thiazine[21] and triazine derivatives[22].

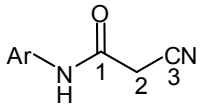


**Figure 1**.

## 2. Results and Discussion

The new starting compound, 4-(2-cyanoacetamido) benzoic acid (**1**) was prepared *via* treatment of *p*-aminobenzoic acid with 1-cyanoacetyl-3,5-dimethyl pyrazole as cyanoacetylation reagent in dry toluene. The structure **1** was established on the basis of spectral data. The IR spectrum revealed absorption band at 3322 cm$^{-1}$ for NH group, broad peak around 3000 cm$^{-1}$ for OH function of the carboxylic group, sharp band at 2260 cm$^{-1}$ for cyano function and a strong broad band at 1695 cm$^{-1}$and 1650 cm$^{-1}$ for two carbonyl groups, respectively. It's $^1$H NMR spectrum (DMSO-$d_6$) revealed the presence of three singlet signals at $\delta$ 3.96 ppm, $\delta$ 10.59 ppm and at $\delta$ 12.77 ppm assignable to the methylene protons, NH proton and carboxylic proton, respectively. Its mass spectrum showed a molecular ion peak at *m/z* = 204 corresponding to a molecular formula ($C_{10}H_8N_2O_3$).

**Scheme 1**

Moreover, Gewald reaction of 4-(2-cyanoacetamido) benzoic acid (1) with elemental sulfur and phenyl isothiocyanate in warming ethanol containing triethylamine as a basic catalyst afforded 4-(4-amino-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carboxamido) benzoic acid (2) (Scheme

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1).

Compound 2 was supported on the basis of spectral data. The IR spectrum showed absence of absorption band assignable to cyano function presence of absorption bands at 3436 and 3386 $cm^{-1}$ due amino group, NH absorption appeared at 3257 $cm^{-1}$ while two strong absorptions appeared at 1699 and 1650 $cm^{-1}$ for two carbonyl groups. It's $^1H$ NMR spectrum (DMSO-$d_6$) revealed the absence of a singlet signal characteristic to methylene protons, while a broad singlet signal for the newly formed amino group was appeared at $\delta$ 5.13 ppm, while, NHCO and COOH protons appeared at $\delta$ 10.2 ppm and $\delta$ 12.82 ppm, respectively. Moreover, the mass spectrum for the thiazole structure 2 showed a molecular ion peak at *m/z* = 371 corresponding to a molecular formula ($C_{17}H_{13}N_3O_3S_2$).

The ketene *S,S*-dithioacetals 3 was prepared by reaction of 4-(2-cyanoacetamido)benzoic acid (1) with carbon disulfide and potassium hydroxide in DMF followed by the alkylation with methyl iodide. The structure of 3 was elucidated on the basis of the elemental analysis and spectral data. The element test showed the presence of sulfur element. The IR spectrums showed the appearance of absorption band at 3355, 2259 $cm^{-1}$ for NH, CN groups, respectively and showed two absorptions for two carbonyl groups at 1692 and 1640 $cm^{-1}$. It's $^1H$ NMR spectrum (DMSO-$d_6$) showed singlet signal at $\delta$ 3.35 ppm for 6 protons of two similar methyl protons, while a singlet signal for the methylene protons was disappeared. Two singlet signals for NH and COOH protons were appeared at $\delta$ 10.64 and $\delta$ 12.79 ppm, respectively. The mass spectrum showed a molecular ion peak at *m/z* = 308 corresponding to a molecular formula ($C_{13}H_{12}N_2O_3S_2$).

Polarized cyanoketene *N,S*-acetals are versatile starting materials for the synthesis of a wide variety of fused heterocycles. So, further reaction of 3 with aniline in refluxing DMF afforded cyanoketene *N,S*-acetals 4.

Compound 4 was also confirmed by alternative synthesis. Thus, when 1 was reacted with phenyl isothiocyanate in DMF containing potassium hydroxide followed by addition of methyl iodide afforded 4-(2-cyano-3-(methylthio)-3-(phenylamino)acrylamido)benzoic acid (4).

The assignment of the structure 4 was based also on the element test and spectral data. The element test showed the presence of sulfur element. The IR spectrum showed absorption bands at 3386, 3255 $cm^{-1}$ for two NH stretching, a band at 2195 $cm^{-1}$ for cyano group, and two strong absorption bands for two carbonyl groups at 1689 and 1640 $cm^{-1}$. Its $^1H$ NMR spectrum (DMSO-$d_6$) displayed no signal for $CH_2$ protons, while a strong singlet signal at $\delta$ 3.23 ppm for methyl protons, two broad signals at $\delta$ 9.21 ppm, $\delta$ 10.25 ppm were appeared for NH-Ph, NHCO protons, respectively, and COOH proton appeared as singlet signal at $\delta$ 12.89 ppm. The mass spectrum showed a molecular ion peak at *m/z* = 353 corresponding to the molecular formula ($C_{18}H_{15}N_3O_3S$).

Compound 4 was utilized as a starting material for preparation of wide variety of fused hetero compounds by reaction with bifunctional nucleophilic reagents. Heating of 4 with hydrazine hydrate afforded pyrazole derivative 5, while refluxing of 4 with hydroxyl amine hydrochloride and sodium carbonate in ethanol afforded isoxazole derivative **6**. Finally, refluxing of 4 with thiourea in DMF afforded pyrimidine derivative **7**. The IR spectrum of **5** displayed stretching bands at 3463 and 3362 $cm^{-1}$ for the formed amino group and three absorption bands for three NH groups at 3291, 3255 and 3223 $cm^{-1}$, while two carbonyl absorptions appeared at 1652 and 1686 $cm^{-1}$. It's $^1H$ NMR spectrum (DMSO-$d_6$) displayed broad signal at $\delta$ 6.23 ppm assignable for new formed amino protons, three broad signals for the three NH protons at $\delta$ 8.62, 9.12 and 10.35 ppm, while COOH proton appeared at $\delta$ 12.59 ppm. The mass spectrum showed a molecular ion peak at *m/z* = 337 corresponding to a molecular formula ($C_{17}H_{15}N_5O_3$). The IR spectrum of **6** displayed stretching bands at 3447 and 3355 $cm^{-1}$ for the formed amino group and two absorption bands for two NH groups at 3328 and 3273 $cm^{-1}$, in addition to two carbonyl absorptions at 1683 and 1657 $cm^{-1}$. It's $^1H$ NMR spectrum (DMSO-$d_6$) exhibited appearance of a broad signal at $\delta$ 5.62 ppm assignable for new formed amino protons, two broad signals for the protons of two NH groups at $\delta$ 9.36 ppm and 10.21 ppm, while COOH proton appeared at $\delta$ 12.80 ppm. The mass spectrum showed a molecular ion peak at *m/z* = 338 corresponding to a molecular formula ($C_{17}H_{14}N_4O_4$).

The $^1H$ NMR(DMSO-$d_6$) spectrum of 7 exhibited a broad signal at $\delta$ 5.35 ppm assignable for newly formed amino protons, three broad signals for the protons of three NH group at $\delta$ 8.80, 9.70 and 10.21 ppm while COOH proton appeared at $\delta$ 12.88 ppm. The mass spectrum showed ~~a~~ the molecular ion peak at *m/z* = 381 compatible with the molecular formula ($C_{18}H_{15}N_5O_3S$).

The active methylene group in the cyanoacetamide derivative 1 readily adds to phenyl isothiocyanate in DMF containing potassium hydroxide to give the non isolable enaminonitrile 8, which underwent heterocyclization upon treatment with $\alpha$-halocarbonyl compounds such as chloroacetyl chloride, bromoacetone and ethyl bromoacetate to afford the corresponding thiazole derivatives 9-11, respectively (Scheme 2). The assignment of the structures 9-11 were based on elemental analysis and spectral data. The element test in general showed the presence of sulfur element. Also, the IR spectra of structures 9-11 displayed absorption band assignable for cyano function and broad peak at 3300 $cm^{-1}$ for COOH function. The IR spectrum of 9 displayed stretching frequencies at 3337 and at 2193 $cm^{-1}$ for the NH and CN frequencies, respectively, three absorptions bands corresponding to three carbonyl groups at 1714, 1689 and 1643 $cm^{-1}$. It's $^1H$ NMR spectrum showed appearance of a signal for methylene protons at $\delta$ 3.16 ppm and two singlet signals at $\delta$ 10.21 and 12.80 ppm for NH and COOH protons, respectively. The IR spectrum of 10 displayed stretching band at 3213, 2212 $cm^{-1}$ for the NH, cyano functions, respectively and two carbonyl absorptions at 1700, 1663 $cm^{-1}$. It's $^1H$ NMR spectrum displayed new signals at $\delta$ 1.80 ppm for methyl protons and a singlet signal at $\delta$ 6.89 ppm assignable for (=CH) proton and two singlet signals at $\delta$ 10.61 and 12.70 ppm for NH and COOH protons,

respectively.

**Scheme 2**

The IR spectrum of 11 displayed stretching band at 3355, 2259 $cm^{-1}$ for the NH and cyano functions respectively, and three carbonyl absorptions at 1723, 1690 and 1641 $cm^{-1}$. It's $^1H$ NMR spectrum showed singlet signals for methylene protons at $\delta$ 3.76 ppm and two singlet signals at $\delta$ 10.22 and 12.60 ppm for NH and COOH protons, respectively. The mass spectrum of compounds 9-11 showed the molecular ion peaks at *m/z* 379, 377 and 379 corresponding to the molecular formulas ($C_{19}H_{13}N_3O_4S$), ($C_{20}H_{15}N_3O_3S$) and ($C_{19}H_{13}N_3O_4S$), respectively.

Reaction of cyanoacetamide derivative 1 with carbon disulfide in boiling DMF containing catalytic amount of potassium hydroxide followed by acidification by hydrochloric acid afforded the dithiol derivative 4-(2-cyano-3,3-dimercaptoacrylamido)benzoic acid 12. The assignment of structure 12 was based on both elemental analysis and spectral data. The element test showed the presence of sulfur element. The IR spectrum displayed absorptions at 3223, 2179, 1695 and 1650 $cm^{-1}$ for NH, cyano and two carbonyl groups, respectively. The $^1H$ NMR spectrum revealed double of doublet at $\delta$ 2.72 and 2.88 ppm for two SH protons, NHCO proton at $\delta$ 10.10 ppm and the carboxylic proton at $\delta$ 12.75 ppm. The mass spectrum showed the molecular ion peak at *m/z* 280 corresponding to the molecular formula ($C_{11}H_8N_2O_3S_2$).

In continuation of our interest with the synthesis of fused hetero compounds, further reaction of 12 with chloroacetyl chloride in boiling DMF afforded 4-[2-cyano-2-(4-oxo-1,3-dithiolan-2-ylidene)acetamido] benzoic acid (13). The structure 13 was confirmed by alternative synthesis. Thus, it was found that reaction of 1 with carbon disulfide in DMF containing potassium hydroxide followed by addition of chloroacetyl chloride afforded 13. The structure of 13 was supported on the basis of elemental analysis and spectral data. Element analysis indicated that sulfur was present. The IR spectrum displayed absorption bands for NH, CN and three carbonyl functions at 3277, 2193, 1720, 1689 and 1643 $cm^{-1}$, respectively. It's $^1H$ NMR spectrum displayed the absence of two signals characteristic to the two SH protons, while singlet signal at $\delta$ 3.20 ppm assignable for the newly methylene protons, in addition to singlet signals for NHCO ,COOH protons at $\delta$ 10.10 and 12.65 ppm, respectively. Moreover, the mass spectrum showed the molecular ion peak at *m/z* 320 corresponding to the molecular formula of ($C_{13}H_8N_2O_4S_2$).

The active methylene group in the dithiolan derivative 13 is too active to be coupled with aromatic diazonium salts. So, benzene diazonium salt underwent coupling reaction with 13 to afford arylazo derivative 14. The structure of 14 was elucidated on the basis of spectral data. The IR spectrum showed the absorption bands at 3317, 3237, 3000, 2260, 1698, 1685 and 1642 $cm^{-1}$ assignable for two NH, OH, CN and three (CO) groups, respectively. It's $^1H$ NMR spectrum showed the absence of a singlet signal assignable for ($CH_2$) protons, while showed a new signal at $\delta$ 11.85 ppm for hydrazo proton in addition to signals at proton $\delta$ 10.21 and 12.62 ppm corresponding to NHCO and COOH protons, respectively. The mass spectrum showed the molecular ion peak at *m/z* 424 corresponding to the molecular formula ($C_{19}H_{12}N_4O_4S_2$).

Gewald reaction of 4-(2-cyanoacetamido)benzoic acid (1) with cyclopentanone and elemental sulfur in boiling ethanol containing a catalytic amount of morpholine as a basic catalyst gave the corresponding thiophene derivative 15 (Scheme 3). Compound 15 was supported on the basis of elemental analysis and spectral data. The IR spectrum displayed no absorption band assignable to cyano function while presence of absorption bands at 3422 and 3386 $cm^{-1}$ assignable to the newly formed amino group, NH absorption was appeared at 3277 $cm^{-1}$, in addition to strong absorptions at 1705 and 1643 $cm^{-1}$ for two carbonyl functions. It's $^1H$-NMR spectrum (DMSO-$d_6$) displayed the disappearance of a singlet signal characteristic to methylene protons while singlet broad signal at $\delta$ 5.69 ppm for the new amino protons in addition to three broad signals at $\delta$ 1.73, 2.89 and 3.68 ppm assignable for aliphatic ring protons. NH and COOH protons were appeared at $\delta$ 10.23 and 12.75 ppm, respectively. Moreover the mass spectrum for the thiophene structure **15** showed a molecular ion peak at *m/z* 302 corresponding to the molecular formula ($C_{15}H_{14}N_2O_3S$).

**Scheme 3**

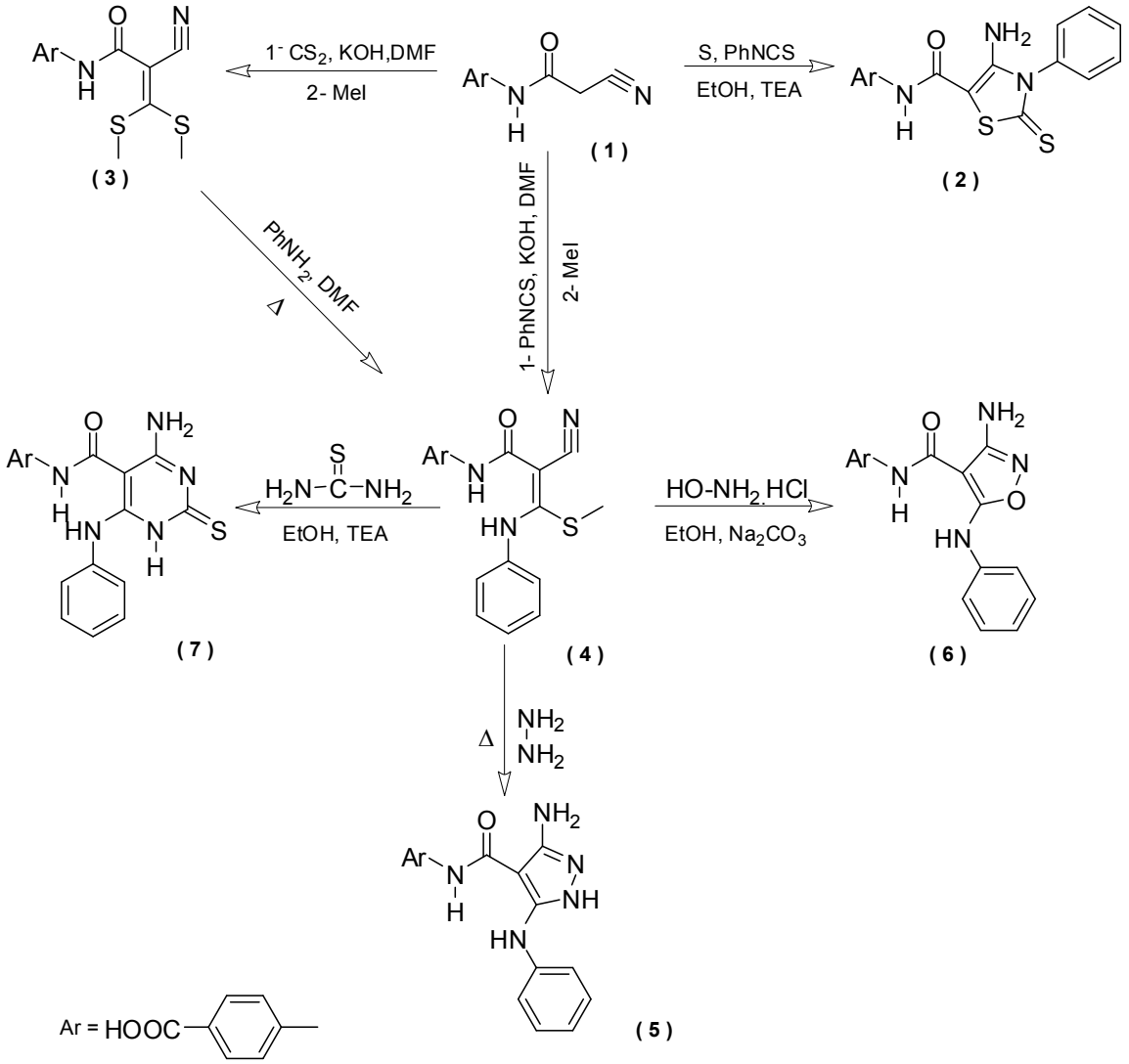
The condensation of cyanoacetamide derivative 1 with salicylaldehyde in ethanol containing a catalytic amount of piperidine under reflux yielded the corresponding coumarin derivative 16. The structure of 16 was established on the basis of spectral data. The IR spectrum revealed the lack of absorption band which belong to CN function and the presence of strong bands at 3447 and 3324 $cm^{-1}$ for two NH groups, two carbonyl absorptions appeared at 1696 and 1643 $cm^{-1}$. Moreover, it's $^1H$-NMR spectrum (DMSO-$d_6$) showed the presence of four singlet signals at $\delta$ 6.24 ppm assignable to methine proton, $\delta$ 8.19 ppm characteristic to the new formed imine proton, (=NH) $\delta$ 10.21 ppm for NH proton and $\delta$ 12.60 ppm for COOH protons, respectively. Furthermore, the mass spectrum showed the molecular ion peak at *m/z* 308 corresponding to a molecular formula ($C_{17}N_{12}N_2O_4$).

To explore the synthetic potentiality of compound 1, the reaction of 1 with $\alpha$-halocarbonyl compounds was investigated. Thus, treatment of 1 with phenacyl bromide in refluxing ethanol containing a catalytic amount of triethylamine afforded 4-(2-cyano-4-oxo-4-phenylbutanamido) benzoic acid (17). The structure of 17 was established on the basis of spectroscopic data. The IR spectrum revealed additional absorption bands for three carbonyl groups appeared at 1723, 1680 and 1644 $cm^{-1}$, while It's $^1H$ NMR spectrum (DMSO-$d_6$) displayed doublet and triplet signals at $\delta$ 2.6 and 3.4 ppm for $CH_2$ and CH groups, respectively, the NH and COOH protons appeared at $\delta$ 10.10 and 12.57 ppm, respectively. The mass spectrum showed the molecular ion peak at *m/z* 322 corresponding to the molecular formula ($C_{18}H_{14}N_2O_4$).

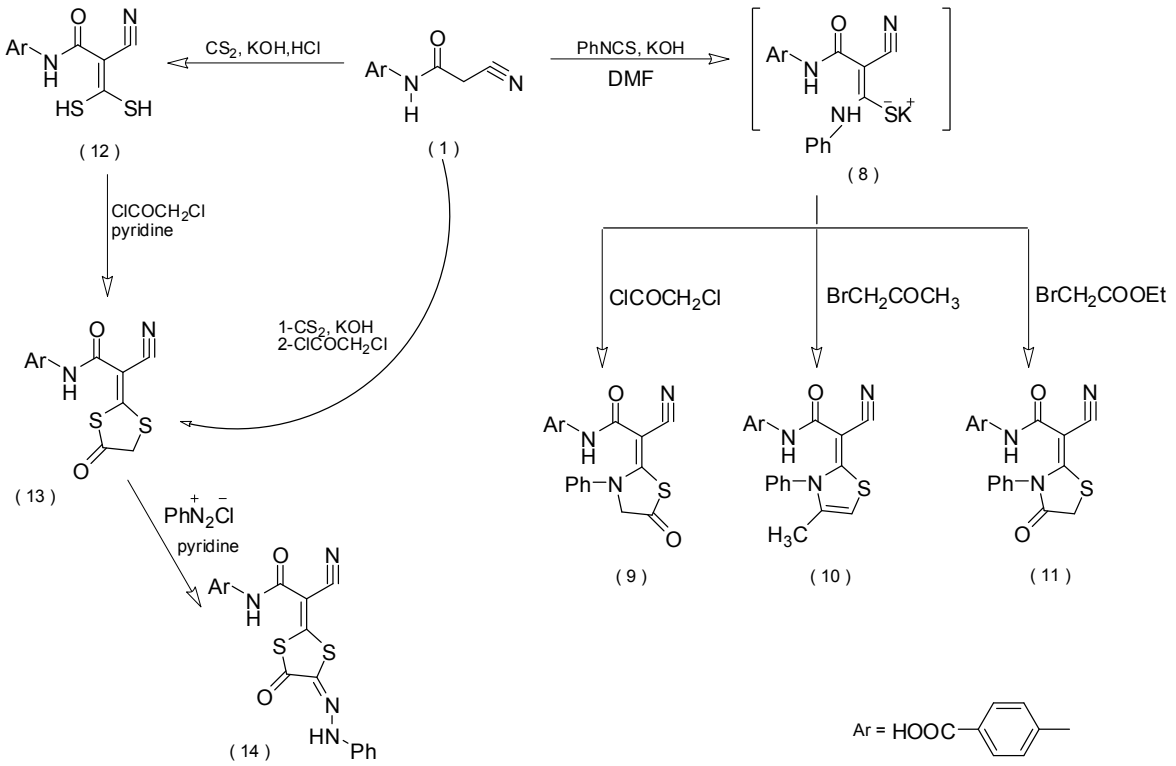
Compound 17 was utilized as a starting material for

further preparation of several hetero rings. Hence, refluxing of 17 with hydroxyl amine hydrochloride in excess amount sodium carbonate or reaction with hydrazine hydrate in presence of catalytic amount of triethylamine in boiling DMF afforded 4-(6-amino-3-phenyl-2*H*-1,2oxazine-5- carboxamido)benzoic acid (18) and 4-(3-amino-6-phenyl-1,2–dihydropyridazine-4-carboxamido)benzoic acid (19), respectively. The structure 18 was established on the basis of spectroscopic data. The IR spectrum showed the disappearance of cyano function while absorption bands at 3422 and 3386 $cm^{-1}$ assignable to the amino group were appeared beside two absorptions bands for two NH functions at 3277 and 3204 $cm^{-1}$. Two absorptions bands assignable for two carbonyl functions were appeared at 1692 and 1643 $cm^{-1}$. It's $^1H$ NMR spectrum (DMSO-$d_6$) revealed no signals for the adjacent $CH_2$ and CH groups. On the other hand, five singlet signal at $\delta$ 6.23 ppm for $NH_2$ protons, at $\delta$ 6.50 ppm for =CH proton, at $\delta$ 10.12, $\delta$ 11.82 and $\delta$ 12.86 ppm for two NH and COOH protons, respectively. The mass spectrum showed the molecular ion peak at *m/z* 337, corresponding to the molecular formula ($C_{18}H_{15}N_3O_4$).

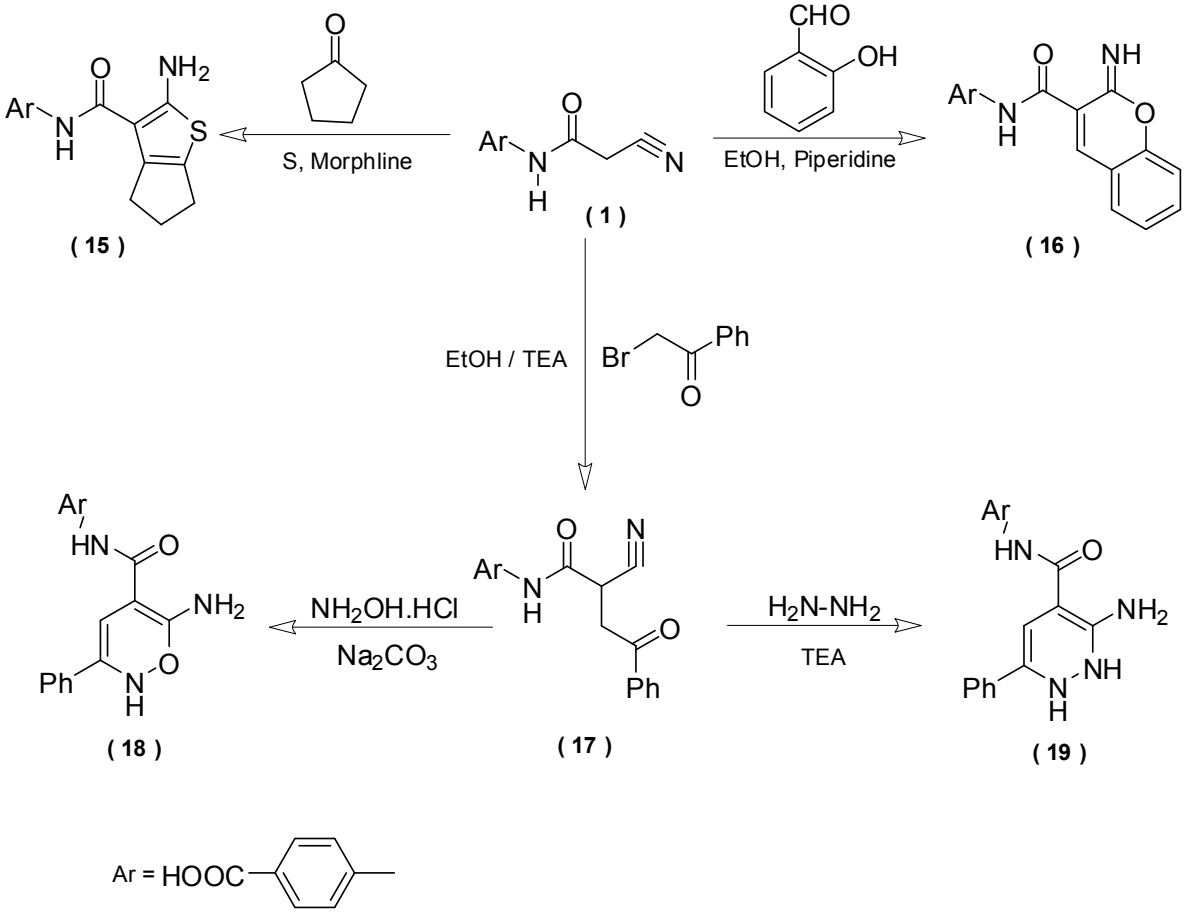
The structure 19 was established on the basis of spectroscopic data. The IR spectrum showed no absorption band assignable to cyano function, while appearing absorption bands at 3447 and 3355 $cm^{-1}$ assignable to the formed amino group, three absorptions for three NH groups at 3328, 3293 and 3273 $cm^{-1}$ in addition to two carbonyl groups absorptions at 1683 and 1645 $cm^{-1}$ were appeared. It's $^1H$ NMR (DMSO-$d_6$) spectrum displayed a singlet broad signal at $\delta$ 5.22 ppm assignable to $NH_2$ protons, singlet signal at $\delta$ 6.53 ppm for =CH proton and three singlet signals for three NH protons at $\delta$ 9.19, 10.46 and 11.94 ppm while a carboxylic proton was appeared at $\delta$ 12.89 ppm. The mass spectrum showed the molecular ion peak at *m/z* 336, corresponding to the molecular formula ($C_{18}H_{16}N_4O_3$).




**Scheme 1.**




**Scheme 2**.




**Scheme 3**.

# 3. Experimental

All melting points (uncorrected) are in degree centigrade and were determined on Gallenkamp electric melting point apparatus and high performance liquid chromatography (HPLC, Shimadzu, Kyoto, Japan) were used to perform general purification procedures. The IR spectra were recorded (KBr) on a Mattson 5000 FTIR spectrophotometer at Microanalytical Unit, Faculty of Science, Mansoura University. The $^1$H NMR spectra were measured on Bruker WP 300 MHz, 200 MHz in DMSO-$d_6$ as solvent, using TMS as an internal reference at Microanalytical Unit, Faculty of Science, Cairo University. Mass spectra were recorded on Finnegan MAT 212 instrument at Microanalytical Unit, Faculty of Science, Cairo University.

**Synthesis of 4-(2-cyanoacetamido)benzoic acid (1)**

A solution of *p*-aminobezoic acid (1.36 g, 0.01 mol) in dry toluene (50 mL) was added to a solution of 1-cyano-acetyl-3,5-dimethylpyrazole (1.63 g, 0.01 mol) in the same solvent (30 mL) and the mixture was heated under reflux for 15 min. After cooling, the solid portion was isolated and recrystallized from dry ethanol to give **1**; white powder; 267-269$^o$C; (90%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3322 (NH), 3000 (OH), 2260 (CN), broad 1695, 1650 (2CO); $^1$H NMR (DMSO) $\delta$ 3.96 (s, 2H, $CH_2$), 7.64-7.95 (dd, 4H, Ar-H), 10.59 (s, 1H, NHCO), 12.77 (s, 1H, COOH). *m/z* 204 ($M^+$, 12.45), 137 (76.89), 120 (15.25), 77 (47.95). Anal. Calcd. for $C_{10}H_8N_2O_3$ (204.1): C 58.82; H 3.95; N 13.72 %. Found: C 58.65; H 3.82; N 13.69 %.

**Synthesis of 4-[(4-amino-3-phenyl-2-thioxo-2,3- dihydro-thiazole-5-carbox-amido)benzoic acid (2)**

To a solution of compound 1 (0. 4 g, 2 mmol) in absolute ethanol (20 mL) containing triethylamine (5 drops), elemental sulfur (0.06 g, 2 mmol) and phenylisothiocyanate (0.27 g, 2 mmol) were added. The reaction mixture was heated at 60°C for 2 h with continuous stirring and then poured onto beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration, dried well, and recrystallized from DMF/ethanol mixture (3:1) to give **2**; white powder; 285-287$^o$C; (60%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3436, 3386 ($NH_2$), 3257 (NH), 3000 (OH), 1699, 1650 (2CO); $^1$H NMR (DMSO) $\delta$ 5.13 (s, 2H, $NH_2$), 7.19-7.95 (m, 9H, Ar-H), 10.20 (s, 1H, NH-CO), 12.82 (s, 1H, COOH). *m/z* 371 ($M^+$, 55.45), 235 (79.3), 215 (23.25), 182 (22.95), 127 (35.5), 77 (53.13). Anal. Calcd. for $C_{17}H_{13}N_3O_3S_2$ (371.4): C 54.97; H 3.53; N 11.31 %. Found: C 54.86; H 3.42; N 11.28 %.

**Synthesis of 4-(2-cyano-3,3-bis(methylthio)- acrylamido) benzoic acid (3)**

To a stirred solution of potassium hydroxide (0.22 g, 4 mmol) in dimethylformamide (20 mL) compound **1** was added (0.8 g, 4 mmol). After stirring for 30 min, carbon disulfide (0.2 mL, 4 mmol) was added to the resulting mixture. Stirring was continued for 12 h, and then methyl iodide (0.3 mL, 4 mmol) was added dropwise. Stirring continued for additional 6 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol to yield **3**; yellow sheets; 345-347$^o$C; (54%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3355 (NH), 3000 (OH), 2259 (CN), 1692, 1640 (2CO); $^1$H NMR (DMSO) $\delta$ 3.35 (s, 6H, $2CH_3$), 7.64-7.95 (dd, 4H, Ar-H), 10.64 (s, 1H, NHCO), 12.79 (s, 1H, COOH); *m/z* 308 ($M^+$, 78.55), 280 (27.25), 190 (66.24), 126 (26.21), 91 (78.13). Anal. Calcd. for $C_{13}H_{12}N_2O_3S_2$ (308.4): C 50.63; H 3.92; N 9.08 %. Found: C 50.65; H 3.85; N 9.12 %.

**Synthesis of (E) - 4-(2 - cyano-3 - (methylthio)-3-(phenyl amino)acrylamido) benzoic acid (4)**

***Method (A):*** A mixture of **3** (0.42 g, 0.01 mol) and aniline (0.1 mL, 0.01 mol) in DMF (25 mL) was heated under reflux for 6 h until the evolution of methylthiol was ceased. The reaction mixture was left to cool and then poured to ice cooled water (100 mL). The solid product that formed was filtered off, dried well and recrystallized from ethanol and DMF mixture (1:5) to yield 4.

**Method (B):** To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL) was added compound **1** (0. 4 g, 2 mmol). After stirring for 30 min, phenylisothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then methyl iodide (0.28 g, 2 mmol) was added, stirring continued for additional 3 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol and DMF mixture (1:5) to yield 4; yellow powder; 245-247$^o$C; (55%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3386, 3255 (2NH), 3000 (OH), 2195 (CN), 1689, 1640 (2CO); $^1$H NMR (DMSO) $\delta$ 3.23 (s, 3H, $SCH_3$), 7.20-7.96 (m, 9H, Ar-H), 9.21 (s, 1H, NH-Ph), 10.25 (s, 1H, NHCO), 12.89 (s, 1H, COOH); *m/z* 353 ($M^+$, 65.25), 306 (45.9), 217 (77.24), 169 (78.1), 137 (47.5). Anal. Calcd. for $C_{18}H_{15}N_3O_3S$ (353.4): C 61.18; H 4.28; N 11.89 %. Found: C 61.24; H 4.21; N 11.96 %.

**Synthesis of 4-(3-amino-5-(phenylamino)-1*H*- pyrazole - 4-carboxamido) benzoic acid (5)**

A mixture of 4 (0.7 g, 2 mmol) and hydrazine hydrate 98% (0.5 mL, 5 mmol) was heated on a steam bath for 1 h then left to cool. The reaction mixture was triturated with ethanol and the resulting solid was filtered off and recrystallized from ethanol/DMF mixture (1:3) to give **5**; white crystals; 240-242°C; (85%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3463, 3362 ($NH_2$), 3291, 3255, 3223 (3NH), 3000 (OH), 1652, 1686 (2CO); $^1$H NMR (DMSO) $\delta$ 6.23 (s, 2H, $NH_2$), 7.19-7.97 (m, 9H, Ar-H), 8.62 (s, 1H, NH), 9.12 (s, 1H, NH-Ph) 10.35 (s, 1H, NH-CO), 12.59 (s, 1H, COOH); *m/z* 337 ($M^+$, 51.22), 215 (27.55), 182 (23.45), 127 (27.54), 77 (75.47). Anal. Calcd. for $C_{17}H_{15}N_5O_3$ (337.3): C 60.53; H 4.48; N 20.76 %. Found: C 60.65; H 4.39; N 20.88 %.

**Synthesis of 4 - (3-amino - 5- (phenylamino)-isoxazole-4-carboxamido) benzoic acid (6)**

A solution of 4 (0.7 g, 2 mmol) in ethanol (30 mL) was treated with hydroxyl amine hydrochloride (0.14 g, 2 mmol) and sodium carbonate (0.43 g ,4 mmol). The reaction mixture was heated under reflux for 3 h, then left to cool. The solid product was collected by filtration, washed several times with water and recrystallized from ethanol to give **6**;

white crystals; 300-302°C; (85%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3447, 3355 ($NH_2$), 3328, 3273 (2NH), 3000 (OH), 1683, 1657 (2CO); $^1$H NMR (DMSO) $\delta$ 5.62 (s, 2H, $NH_2$), 7.18-7.98 (m, 9H, Ar-H), 9.36 (s, 1H, NH-Ph), 10.21 (s, 1H, NHCO), 12.80 (s, 1H, COOH); *m/z* 338 ($M^+$, 53.24), 301 (48.57), 215 (28.22), 182 (17.54), 127 (28.24), 77 (51.32). Anal. Calcd. for $C_{17}H_{14}N_4O_4$ (338.3): C 60.35; H 4.17; N 16.56 %. Found: C 60.43; H 4.12; N 16.63 %.

**Synthesis of 4-(4-amino-6-(phenylamino)-2-thioxo - 1,2 - dihydropyrimidine-5-carboxamido)benzoic acid (7)**

A solution of **4** (0.7 g, 2 mmol) in ethanol (20 mL) containing triethylamine (0.5 mL) was treated with solution of thiourea (0.15 g, 2 mmol) in ethanol (10 mL). The reaction mixture was heated under reflux for 10 h, then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol to give **7**; white sheets; 320-322°C; (80%); $^1$H NMR (DMSO) $\delta$ 5.35 (s, 2H, $NH_2$), 7.18-7.93 (m, 9H, Ar-H), 8.80 (s, 1H, NH), 9,70 (s, 1H, NH-Ph), 10.21 (s, 1H, NH-CO), 12.88 (s, 1H, COOH); *m/z* 381 ($M^+$, 65.21), 267 (40.12), 215 (48.56), 182 (27.24), 136 (80.14), 91 (55.72), 77 (65.89). Anal. Calcd. for $C_{18}H_{15}N_5O_3S$ (381.4): C 56.68; H 3.96; N 18.36 %. Found: C 56.74; H 3.83; N 18.42 %.

**Synthesis of (*E*)-4-[2-cyano-2-(5-oxo-3-phenyl thiazolidin -2-ylidene)acet-amido]benzoic acid (9)**

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL), compound 1 was added (0. 4 g, 2 mmol). After stirring for 30 min, phenylisothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h. Then chloroacetyl chloride (0.16 mL, 2 mmol) was added. Stirring continued for additional 3 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol to yield **9**; pale yellow powder; 320-322°C; (65%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3337 (NH), 3000 (OH), 2193 (CN), 1714, 1689, 1643 (3CO); $^1$H NMR (DMSO) $\delta$ 3.16 (s, 2H, $CH_2$), 7.19-7.93 (m, 9H, ArH), 10.21 (s, 1H, NHCO), 12.80 (s, 1H, COOH); *m/z* 379 ($M^+$+1, 51.24), 215 (80.25), 169 (20.55), 132 (30.58), 77 (70.13). Anal. Calcd. for $C_{19}H_{13}N_3O_4S$ (379.4): C 60.15; H 3.45; N 11.08 %. Found: C 60.27; H 3.55; N 11.11 %.

**Synthesis of (*E*)-4-[2-cyano-2-(4-methyl-3- phenylthiazol -2-(*3H*)-ylidene) acetamido]benzoic acid (10)**

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL) compound **1** was added (0.4 g, 2 mmol). After stirring for 30 min, phenylisothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h, and then bromoacetone (0.3 mL, 2 mmol) was added. Stirring continued for additional 3 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol to yield **10**; pale brown powder; 300-302°C; (55%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3213 (NH), 3000 (OH), 2112 (CN), 1700, 1663 (2CO); $^1$H NMR (DMSO) $\delta$ 1.80 (s, 3H, $CH_3$), 6.89 (s, 1H, =CH), 7.12-7.615 (m, 9H, Ar-H), 10.61 (s, 1H, NHCO), 12.70 (s, 1H, COOH); *m/z* 377 ($M^+$, 26.33), 379 (37.85), 215 (68.54), 169 (23.51), 132 (33.54), 91 (76.88), 77 (54.23). Anal. Calcd. for $C_{20}H_{15}N_3O_3S$ (377.4): C 63.65; H 4.01; N 11.13 %. Found: C 63.78; H 4.13; N 11.26 %.

**Synthesis of (*E*)-4-[2-cyano-2-(4-oxo-3-phenyl thiazolidin -2-ylidene) acetamido]benzoic acid (11)**

To a stirred solution of potassium hydroxide (0.11 g, 2 mmol) in dimethylformamide (20 mL) compound 1 was added (0. 4 g, 2 mmol). After stirring for 30 min, phenyl isothiocyanate (0.27 g, 2 mmol) was added to the resulting mixture. Stirring was continued for 6 h and then ethylbromoacetate (0.3 mL, 2 mmol) was added. Stirring continued for additional 3 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol to yield 11; yellow powder; 290-292°C; (66%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3355 (NH), 3000 (OH), 2259 (CN), 1723, 1690, 1641 (3CO); $^1$H NMR (DMSO) $\delta$ 3.76 (s, 2H, $CH_2$), 7.39-7.90 (m, 9H, Ar-H), 10.22 (s, 1H, NHCO), 12.60 (s, 1H, COOH); *m/z* 379 ($M^+$+1, 57.2), 306 (51.5.3), 202 (81.2), 169 (85.3), 137 (79.89), 77 (75.2). Anal. Calcd. for $C_{19}H_{13}N_3O_4S$ (379.4): C 60.15; H 3.45; N 11.08 %. Found: C 60.24; H 3.39; N 11.16 %.

**Synthesis of 4 - (2 - cyano-3,3 - dimercaptoacrylamido) benzoic acid (12)**

To a stirred solution of potassium hydroxide (0.22 g, 4 mmol) in dimethylformamide (20 mL) was added compound **1** (0.8 g, 4 mmol). After stirring for 30 min, carbon disulfide (0.2 mL, 4 mmol) was added to the resulting mixture. Stirring was continued for 12 h and then hydrochloric acid (10 mL, 2 M) was added dropwise. Stirring continued for additional 1 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol to yield **12**; red yellow powder; 291-293°C; (45%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3223 (NH), 3000 (OH), 2179 (CN), 1695, 1605 (2CO); $^1$H NMR (DMSO) $\delta$ 2.72, 2.88 (dd, $J$ = 6.0, 7.7 Hz, 2H, SH), 6.97-7.72 (dd, 4H, Ar-H), 10.10 (s, 1H, NHCO), 12.75 (s, 1H, COOH); *m/z* 280 ($M^+$, 22.10), 204 (17.25), 137 (16.34), 120 (15.89), 76 (80.22). Anal. Calcd. for $C_{11}H_8N_2O_3S_2$ (280.3): C 47.13; H 2.88; N 9.99 %. Found: C 47.21; H 2.83; N 10.04 %.

**Synthesis of (*Z*)-4-[2-cyano-2-(4-oxo - 1,3 - dithiolan - 2 - ylidene)acetamido] benzoic acid (13)**

***Method (A)***: To a stirred solution of potassium hydroxide (0.22 g, 4 mmol) in dimethylformamide (20 mL) compound 1 was added (0.8 g, 4 mmol). After stirring for 30 min, carbon disulfide (0.2 mL, 4 mmol) was added to the resulting mixture. Stirring was continued for 12 h, and then chloroacetyl chloride (0.45 mL, 4 mmol) was added dropwise. Stirring continued for additional 6 h. Then, the reaction mixture was poured onto ice water. The solid product that formed was filtered off, dried and recrystallized from ethanol to yield **13**.

***Method (B)***: To a cooled solution of 12 (1.3 g, 4 mmol) in pyridine (10 mL), chloroacetyl chloride (0.32 mL, 4 mmol) was added dropwise. The reaction mixture was stirred for 5 h, and then was poured onto ice water (100 mL) with drops of HCl. The solid product that formed was filtered off, washed well, dried and recrystallized from ethanol to yield 13; white

sheets; 300-302°C; (45%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3277 (NH), 3000 (OH), 2193 (CN), 1720, 1689, 1643 (3CO); $^1$H NMR (DMSO) $\delta$ 3.20 (s, 2H, $CH_2$), 6.97-7.72 (dd, 9H, Ar-H), 10.10 (s, 1H, NHCO), 12.65 (s, 1H, COOH); *m/z* 320 ($M^+$+1, 17.24), 255 (10.55), 202 (75.24), 187 (27.25), 105 (51.24), 77 (49.22). Anal. Calcd. for $C_{13}H_8N_2O_4S_2$ (320.3): C 48.74; H 2.52; N 8.74 %. Found: C 48.79; H 2.48; N 8.78 %.

**Synthesis of 4-{(Z) - 2 - cyano-2-[(E)-4-oxo- 5 -(2-phenyl hydrazono)-1,3-dithiolan-2-ylidene]acetamido}benzoic acid (14)**

To a solution of **13** (1.3 g, 4 mmol) in pyridine (5 mL), an ice-cooled solution of the aniline diazonium salt [prepared by addition of a solution of sodium nitrile (0.7 g, 8 mmol) in water (5 mL) to aniline (0.1 mL, 4 mmol) in concentrated HCl (3 mL)]was added dropwise with stirring for 30 min, after which water was added and the precipitate product was filtered, washed with water, dried well and recrystallized from ethanol and DMF mixture (1:5) to yield 14; dark brown powder; 270-272°C; (70%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3317, 3237 (2NH), 3000 (OH), 2260 (CN), 1698, 1685, 1642 (3CO); $^1$H NMR (DMSO) $\delta$ 7.19-7.35 (m, 9H, Ar-H), 10.21 (s, 1H, NHCO), 11.85 (s, 1H,=NNH), 12.62 (s, 1H, COOH); *m/z* 424 ($M^+$, 35.21), 330 (65.25), 202 (75.56), 187 (26.55), 137 (79.88), 77 (45.12). Anal. Calcd. for $C_{19}H_{12}N_4O_4S_2$ (424.5): C 53.76; H 2.85; N 13.20 %. Found: C 53.84; H 2.80; N 13.31 %.

**Synthesis of 4- (2-amino-5,6-dihydro - 4*H*-cyclopenta[*b*] thiophene-3-carbox-amido)benzoic acid (15)**

To a solution of compound 1 (0.4 g, 2 mmol) in ethanol (20 mL) containing morpholine (0.5 mL), elemental sulfur (0.064 g, 2 mmol) and cyclopentanone (0.16 mL, 2 mmol) were added. The reaction mixture was heated at 60°C for 2 h with continuous stirring and then poured onto beaker containing an ice/water mixture containing few drops of hydrochloric acid. The formed solid product was collected by filtration, dried well, and recrystallized from DMF and ethanol mixture (3:1) to give compound **15**; yellowish white powder; 225-227°C; (50%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3422, 3386 ($NH_2$), 3277 (NH), 3000 (OH), 1705, 1643 (2CO); $^1$H NMR (DMSO) $\delta$ 1.73 (bs, 2H, $CH_2$), 2.89 (bs, 2H, $CH_2$), 3.68 (bs, 2H, $CH_2$), 5.69 (s, 2H, $NH_2$), 7.74-7.89 (dd, 4H, Ar-H), 10.32 (s, 1H, NHCO), 12.75 (s, 1H, COOH); *m/z* 302 ($M^+$, 45.3), 245 (52.6), 215 (53.2), 169 (19.6), 132 (28.9), 77 (67.2). Anal. Calcd. for $C_{15}H_{14}N_2O_3S$ (302.3): C 59.59; H 4.67; N 9.27 %. Found: C 59.68; H 4.62; N 9.33 %.

**Synthesis of 4 - (2 - imino-*2H*-chromene-3-carboxamido) benzoic acid (16)**

To a solution of compound **1** (0.4 g, 2 mmol) in ethanol (20 mL) containing piperidine (5 drops) and salicyaldehyde (0.3 g, 2 mmol) was added. The reaction mixture was heated under reflux for 1 h, and then allowed to cool. The precipitate that formed was filtered off, washed with ethanol, dried and recrystallized from mixture of DMF and ethanol mixture (1:3) to afford 16; yellow fluorescent crystal; 315-317°C; (70%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3447, 3324 (2NH), 3000 (OH), 1696, 1643 (2CO); $^1$H NMR (DMSO) $\delta$ 6.24 (s, H, =CH), 7.19-7.97 (m, 9H, Ar-H), 8.19 (s, 1H, =NH), 10.21 (s, 1H, NHCO), 12.60 (s, 1H, COOH); *m/z* 308 ($M^+$+1, 5.45), 307 ($M^+$, 79.3), 172 (63.25), 145 (82.95), 120 (65.5), 77 (43.13). Anal. Calcd. for $C_{17}H_{12}N_2O_4$ (308.3): C 66.23; H 3.92; N 9.09 %. Found: C 66.31; H 3.89; N 9.12 %.

**Synthesis of 4 - (2 - cyano-4-oxo-4 - phenylbutanamido) benzoic acid (17)**

A mixture of compound 1 (0.4 g, 2 mmol) and phenacyl bromide (0.39 g, 2 mmol) in ethanol (30 mL) containing triethylamine (5 drops) was heated under reflux for 1 h. The formed solid product was filtered off, washed with ethanol, dried and recrystallized from mixture of DMF and ethanol mixture (1:3) to give 17; white crystals; 180-183°C; (80%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3355 (NH), 3000 (OH), 2250 (CN), 1723, 1680, 1644 (3CO); $^1$H NMR (DMSO) $\delta$ 2.6 (d, $J$ = 7.2 Hz, 2H, $CH_2$), 3.4 (t, $J$ = 7.7 Hz, 1H, CH), 7.67-7.97 (m, 9H, Ar-H), 10.10 (s, 1H, NHCO), 12.57 (s, 1H, COOH); *m/z* 322 ($M^+$+1, 5.25), 322 ($M^+$, 35.23), 255 (15.3), 187 (33.26), 105 (72.65), 85 (51.5). Anal. Calcd. for $C_{18}H_{14}N_2O_4$ (322.3): C 67.07; H 4.38; N 8.69 %. Found: C 67.14; H 4.42; N 8.75 %.

**Synthesis of 4 - (6 - amino- 3 –phenyl -*2H*-1,2-oxazine-5-carboxamido) benzoic acid (18)**

To a solution of **17** (3.2 g, 0.01 mol) in DMF (20 mL), hydroxylamine hydrochloride (0.7 g, 0.01 mol), sodium carbonate (5 g, 0.02 mol) were added. The reaction mixture was heated under reflux for 4 h and then left to cool. The reaction mixture was poured onto ice cooled water (100 mL) the resulting solid was filtered off, dried well and re-crystallized from ethanol/DMF mixture (1:3) to yield compound 18; white crystals; 296-298°C; (53%); IR (KBr)$\nu_{max.}$ cm$^{-1}$: 3422, 3386 ($NH_2$), 3277, 3204 (NH), 3000 (OH), 1692, 1643 (2CO); $^1$H NMR (DMSO) $\delta$ 6.23 (s, 1H, $NH_2$), 6.50 (s, 1H, =CH), 7.16-7.85 (m, 9H, Ar-H), 10.12 (s, 1H, NH-CO), 11.82 (s, 1H, NH), 12.86 (s, 1H, COOH); *m/z* 337 ($M^+$, 50.25), 215 (79.3), 215 (55.81), 169 (22.95), 137 (65.5), 77 (73.13). Anal. Calcd. for $C_{18}H_{15}N_3O_4$ (337.3): C 64.09; H 4.48; N 12.46%. Found: C 64.18; H 4.51; N 12.49%.

**Synthesis of 4 - (3 – amino – 6 – phenyl - 1,2 – dihydro - pyridazine-4-carboxamido) benzoic acid (19)**

A mixture of **17** (3.23 g, 0.01 mol) and hydrazine hydrate 98% (2 mL, 0.02 mmol) was refluxed for 7 h. The reaction mixture was left to cool at room temperature, then was poured onto ice cooled water (100 mL) the resulting solid was filtered off, dried well and recrystallized from ethanol/ DMF mixture (1:3) to yield compound 19; pale yellow crystals; 279-281°C; (65%); IR (KBr)$\nu_{max.}$cm$^{-1}$: 3447, 3355 ($NH_2$), 3328, 3293, 3273 (3NH), 3000 (OH), 1683, 1645 (2CO); $^1$H NMR (DMSO) $\delta$ 5.22 (s, 2H, $NH_2$), 6.53 (s, 1H, =CH), 7.19-7.98 (m, 9H, Ar-H), 9.19 (s, 1H, NH), 11.94 (s, 1H, NH), 10.46 (s, 1H, NHCO), 12.89 (s, 1H, COOH); *m/z* 336 ($M^+$, 65.22), 217 (59.33), 169 (11.15), 137 (62.55), 77 (43.13). Anal. Calcd. for $C_{18}H_{16}N_4O_3$ (336.3): C 64.28; H 4.79; N 16.66%. Found: C 64.33; H 4.82; N 16.69%.

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