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Synthesis and Cytotoxic Evaluation of Some Novel 6-(Benzofuran-2-yl)-4-(4-Fluorophenyl) Pyridines

Magdy I. El-Zahar, Somaia S. Abd EL-Karim and Mogedda E. Haiba

Department of Therapeutical Chemistry, National Research Centre, Dokki, Cairo, Egypt

Abstract: A series of novel substituted benzofuran-2-ylpyridines 1-17 have been synthesized using 2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy] acetohydrazide (3) as starting material. The cyclization of 3 with carbondisulphide, ethylacetoacetate, acetylacetone, diethylmalonate and/or ammonium thiocyanate gave the corresponding derivatives 4-12. Also compound 3 condensed with different aldehydes, acid anhydrides, halogenated compounds and/or isothiocyanate derivatives to give the corresponding derivatives 13-17. The cytotoxic activity of some of these newly synthesized compounds was evaluated against human liver carcinoma cell line (HEPG2).

Key words: Benzofuran · 4-fluorophenyl pyridine · Acetohydrazide · Cytotoxicity · HEPG-2 · Cell line.

INTRODUCTION

Cytotoxic drugs remain the mainstay of cancer chemotherapy and are being administered with novel ways of therapy such as inhibitors of signals [1]. It is therefore important to discover novel cytotoxic agents with spectra of activity and toxicity that differ from those current agents [1, 2]. On the other hand, benzofuran ring system incorporated with different heterocyclic moieties has wide spectrum of anticancer against different types of carcinoma [3-8]. The ability of many compounds containing pyridine moiety to exhibit antitumor activity has been documented in numerous publications and reviews [9-13] especially those containing a cyano group [14-16]. The design of the new prepared compounds based on structurally containing other biologically actives heterocycles or side chains reported in the field of cancer therapy such as triazoles [17-18], oxadiazoles [19-20], pyrazoles [21, 22], pyrroles [23] and Schiff's bases [24-26].

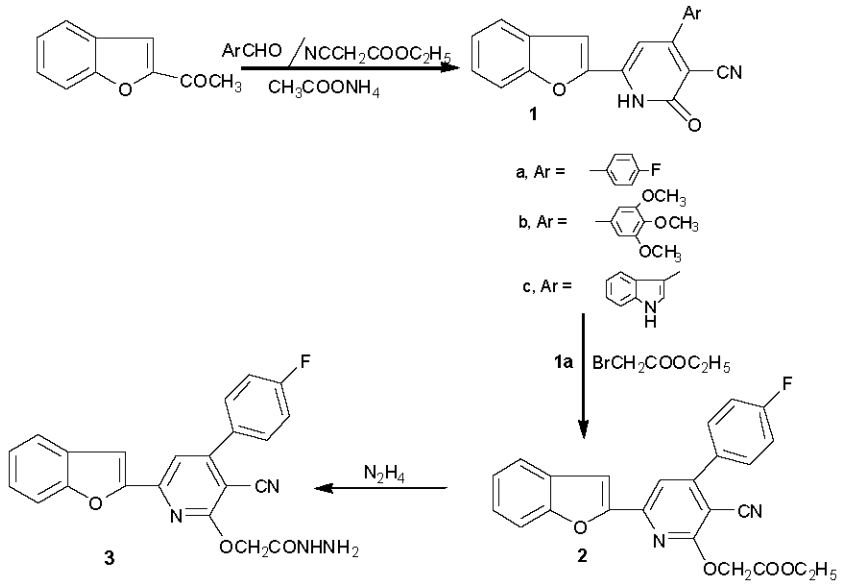
RESULTS AND DISCUSSION

Chemistry: One pot reaction [26] of 2-acetylbenzofuran [27] with different aldehydes namely 4-fluorobenzaldehyde, 3, 4, 5-trimethoxy benzaldehyde and/or indole-3-carboxaldehyde and Ethylcyanoacetate in excess anhydrous ammonium acetate afforded the cyanopyridone derivatives 1a-c respectively. Condensation of 1a with ethylbromoacetate gave ethyl-2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]acetate (2) which condensed with hydrazine hydrate (98%) in ethanol to give 2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy] acetohydrazide (3) which is very useful starting material for the synthesis of all target compounds in this work. (Scheme 1).

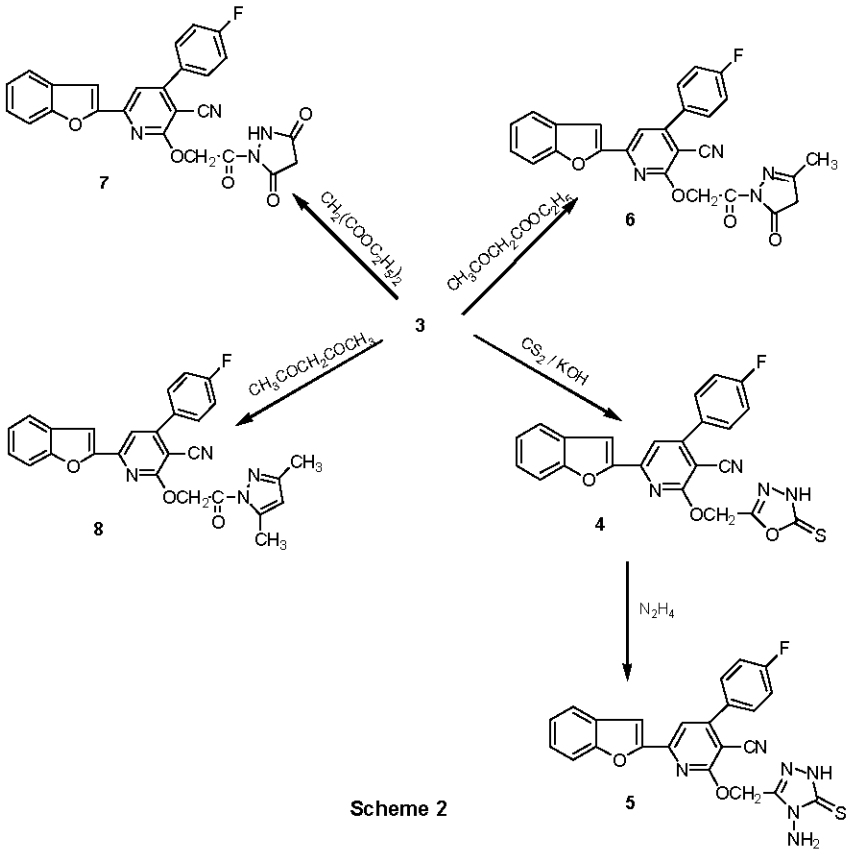
Cyclization of 3 using carbon disulphide in alcoholic potassium hydroxide gave the corresponding oxadiazole-2-thione derivative 4 which converted to 1-aminotriazole -2-thione derivative 5 through condensation with hydrazine hydrate. Also, cyclization of 3 with ethylacetoacetate, diethylmalonate and/or acetylacetone afforded the corresponding pyrazole derivatives 6-8 respectively according to reported methods [28] (Scheme 2).

Moreover, fusion of 3 with ammonium thiocyanate gave the corresponding 2-mercaptotriazole derivative 9 which condensed with diethylaminoethylchloride-HCl in alcoholic sodium hydroxide solution (1%) to give compound 10. Also compound 9 that cyclized either with chloroacetic acid or a mixture of chloroacetic acid and aromatic aldehyde namely anisaldehyde and/or 3,4,5-trimethoxybenzaldehyde to give the corresponding thiazolotriazole derivatives 11, 12a,b respectively according to reported methods [28] (Scheme 3).

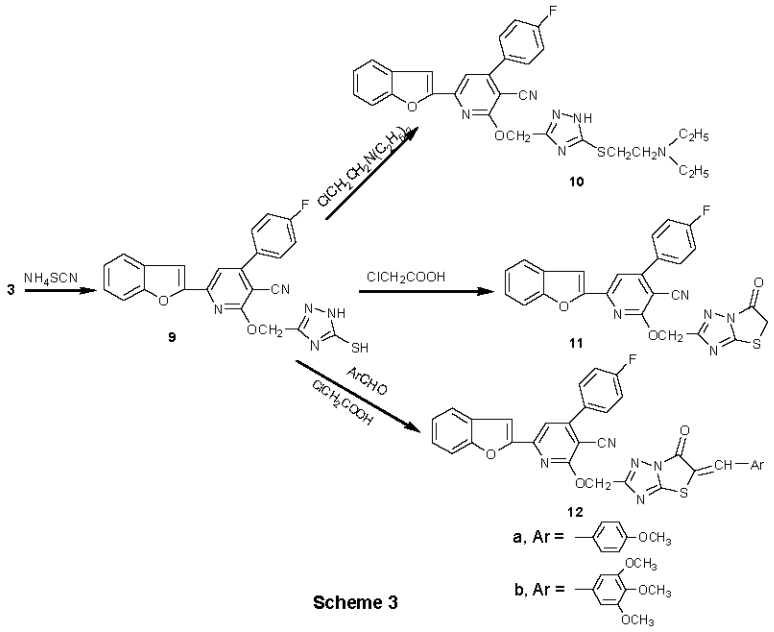
Corresponding Author: Dr. Magdy I. El-Zahar, Department of Therapeutical Chemistry, National Research Centre, Dokki, Cairo, Egypt



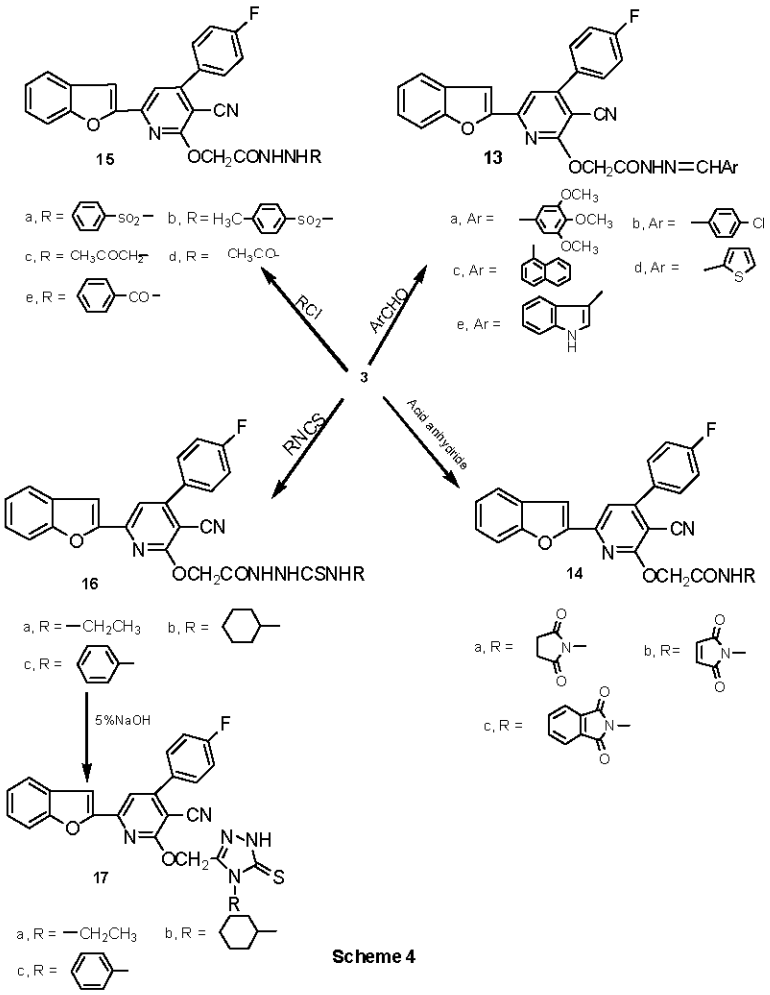
Scheme 1



Scheme 2



Scheme 3



Scheme 4

To get a new series of expected biologically active Schiff's bases it was of interest to condense compound 3 with different aromatic aldehydes namely 3,4,5-trimethoxybenzaldehyde, p-chlorobenzaldehyde, naphthalene-1-carboxaldehyde, thiophene-2-carboxaldehyde and/or indole-3-carboxaldehyde in ethanol to give the corresponding Schiff's bases 13a-e respectively. While the reaction of 3 with different acid anhydride namely succinic anhydride, maleic anhydride and/or phthalic anhydride in acetic acid gave the corresponding N-amide derivatives 14a-c. The reaction of 3 with different halo compounds namely benzene sulphonyl chloride, p-toluenesulphonyl chloride, chloro acetone, acetyl chloride and/or benzoyl chloride in ethanol gave the corresponding N-alkyl or aryl derivatives 15a-e. While the condensation of 3 with different alkyl or aryl isothiocyanate in dimethyl formamide give the corresponding thiosemicarbazide derivatives 16a-c that cyclized with 5% alcoholic sodium hydroxide gave the corresponding N-alkyl or aryl triazolethione derivatives 17a-c (Scheme 4).

Antitumor Screening: In the present work ten selected compounds related to novel (benzofuran-2-yl)-4-(4-fluorophenyl)pyridine derivatives were evaluated as inhibitors of the growth of liver cancer (HEPG2) cell line as a trial to get more effective and less toxic agent.

MATERIALS AND METHODS

Preliminary experiments were done using the human tumor cell line to identify the potential toxicity of ten selected newly synthesized compounds (3, 4, 6, 9, 11, 12a, 13a, 14a, 15b and 16b) in comparison to the known anticancer drugs 5-Flurouracil and Doxorubicin by SRB using Skehan *et al* method [29].

- Cells were plated in 96-multiwell plate (10^4cells/well) for 24 hrs before treatment with compounds to allow attachment of cell to the wall of the plate.
- Different concentration of the compound under test (0, 1, 2.5,5 and 10 μg/ml) were added to the cell monolayer triplicate wells were prepared for each individual dose. Each concentration is evaluated three times (each dose is incubated with the cells in three different wells)
- Monolayer cells were incubated with the compounds for 48 hrs at 37°C and in atmosphere of 5% CO_2.
- After 48 hrs, cells were fixed, washed and stained with Sulfo-Rhodamine-B stain.
- Excess stain was washed with acetic acid and attached stain was recovered with Tris EDTA buffer.
- Color intensity was measured in an ELISA reader.
- The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after the specified compound.

CONCLUSION

The antitumor activity results indicated that all the ten derivatives showed antitumor activity against the tested liver cancer (HEPG2) cell line but with varying intensities in comparison to the known anticancer drugs: 5-Flurouracil and Doxorubicin. Moreover compounds 16b, 4, 3 and 12a showed the highest cytotoxic activity (IC50 equals 3.74, 3.92, 4.1 and 4.31 μg/ml respectively) which were more effective than 5-Flurouracil (IC50 equal 5 μg/ml) (Table 1).

Results were illustrated in Fig. 1 for the cytotoxic activities of the compounds (3, 4, 6, 9 and 11) and in Fig. 2 for the cytotoxic activities of the compounds (12a, 13a, 14a, 15b and 16b) in comparison to 5-Flurouracil and Doxorubicin.

EXPERIMENTAL: All melting points are uncorrected and were taken in open capillary tubes using sulfuric acid and by using electrothermal apparatus. Elemental microanalyses were done by the Microanalytical Laboratory Services, National Research Centre, Dokki, Cairo, Egypt and were found within ±0.5% of the theoretical values. Infrared spectra were recorded on

Table 1: Effect of some selected newly synthesized compounds on liver carcinoma cell line (HEPG2)

Comp.	IC_{50}
5-Flurouracil	5 μg/ml
Doxorubicin	3.65 μg/ml
3	4.1 μg/ml
4	3.92 μg/ml
6	8.54 μg/ml
9	6.53 μg/ml
11	8.48 μg/ml
12a	4.31 μg/ml
13a	9.38 μg/ml
14a	7.43 μg/ml
15b	6.59 μg/ml
16b	3.74 μg/ml

IC50: dose of the compounds which reduces survival to 50%

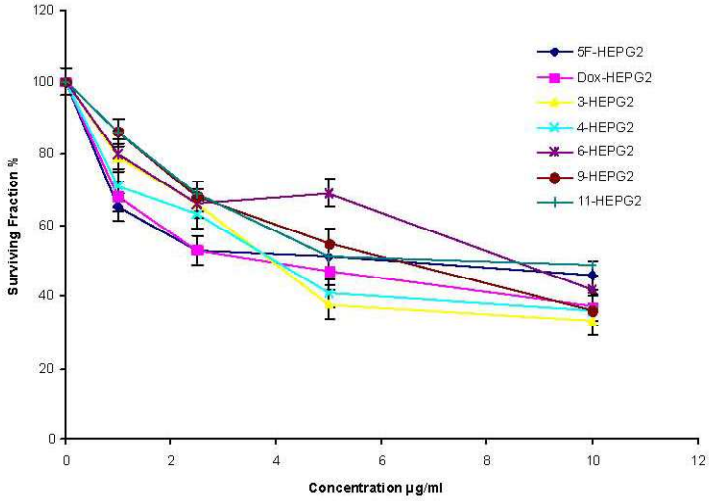


Fig. 1: Cytotoxic effect of compounds 3,4,6,9 and 11 on liver cancer HEPG2 compared to 5- Flurouracil and Doxorubicin

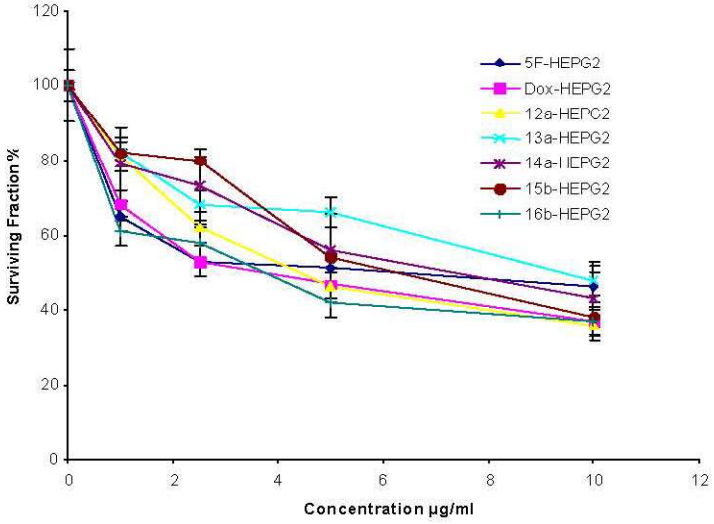
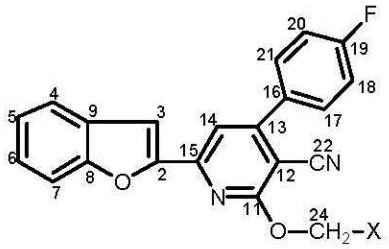


Fig. 2: Cytotoxic effect of compounds 12a,13a,14a,15b and 16b on liver cancer HEPG2 compared to 5- Flurouracil and Doxorubicin

FT/IR-330E, Fourier transform, Infrared spectrometer at cm^{-1} scale by using KBr disc technique. ^{1}H- and ^{13}C NMR spectra were determined by using A JEOl EX-270 NMR spectrometer 270 MHz and measured in δ scale using TMS as an internal standard and the numbering of carbon atoms of benzofuran, pyridine and flourophenyl moieties is given below for sake of comparability. Mass spectra were measured by using mass spectrometer Finnigan MAT SSQ-7000. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminium sheets (Type 60, F 254, Merck, Darmstadt, Germany) and the spots were detected by exposure to UV lamp at λ_{254} nanometer for few seconds.

The chemical names given to the prepared compounds are according to the IUPAC system.



6-(Benzofuran-2-yl)-1, 2-dihydro-4-susbtitute-2-oxopyridine-3-carbonitrile (1a-c)

General procedure: A mixture of 2-acetylbenzofuran (1.6g, 0.01 mol), ethylcyanoacetate (1.2 mL, 0.01mol), anhydrous ammonium acetate (6.16g, 0.08mol) and the appropriate aldehyde, namely, 4-fluorobenzaldehyde, 3,4,5-trimethoxybenzaldehyde and/or indole-3-carboxaldehyde (0.01 mole) in 10 mL n-butanol was heated under reflux for 3-5h. The formed precipitate on cooling was filtered, dried and recrystallized from proper solvent to give compounds 1a-c respectively.

***6-(Benzofuran-2-yl)-4-(4-fluorophenyl)-1, 2-dihydro-2-oxopyridine-3-carbonitrile (1a)*:** Yield 63%, M.P.350-352°C (acetic acid). IR (KBr) cm^{-1}. 3142 (NH), 2219 (C≡N), 1630 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 7.31-7.79 (m, 10H, Ar-H, pyridone H5), 8.10 (s, 1H, NH, exchangeable by D_2O) ^{13}C-NMR (DMSO-d_6) δ: 108.99 (C_3), 111.56 (C_{14}), 113.62 (C_7), 114.69 ($C_{18,20}$), 115.11 (C_{12}), 115.70 (C_{22}), 116.41 (C_4), 122.54 (C_5), 124.64 (C_9), 126.74 (C_6), 127.67 ($C_{17,21}$), 131.41 (C_{16}), 134.82 (C_{15}), 152.44 (C_8), 155.71 (C_2), 161.8 (C_{11}), 163.02 (C_{19}), 165.80 (C_{13}). MS m/z (%): 330 [M^+] (100), 331 [M+1] (23), 302 [M-CO] (15), Anal. Calcd. For $C_{20}H_{11}FN_2O_2$ (330.31): C, 72.72; H, 3.36; N, 8.48, Found: C, 72.31; H, 3.51; N, 8.22.

***6-(Benzofuran-2-yl)-1,2-dihydro-4-(3,4,5-trimethoxyphenyl)-2-oxopyridine-3-carbonitrile (1b)*:** Yield 51%, M.P. 353-355°C (acetic acid). IR (KBr) cm^{-1}. 3115 (NH), 2839 (CH_3), 2218 (C≡N), 1648 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.98 (s, 9H, 3(OCH_3), 6.98-8.15 (m, 9H, Ar-H, pyridone H5, NH, exchangeable by D_2O). MS m/z (%): 402 [M^+] (79), 387 [M-NH] (36), 53 [C_4H_5] (100), Anal. Calcd. For $C_{23}H_{18}N_2O_5$ (402.40): C, 68.65; H, 4.51; N, 6.96, Found: C, 68.32; H, 4.22; N, 6.66.

***6-(Benzofuran-2-yl)-1, 2-dihydro-4-(1H-indol-3-yl)-2-oxopyridine-3-carbonitrile (1c)*:** Yield 69%, M.P. 383-385°C (acetic acid). IR (KBr) cm^{-1}. 3269 (NH), 3115 (NH, amide), 2213 (C≡N),1648 (C=O). ^{1}H-NMR ($CDCl_3$)δ: 7.11-8.21 (m, 12H, Ar-H, pyridone H5, NH, exchangeable by D_2O), 10.21(S, 1H, NH, indole ring exchangeable by D_2O) MS m/z (%): 351 [M^+] (82), 63 [C_4HN] (100), Anal. Calcd. For $C_{22}H_{13}N_3O_2$ (351.36): C, 75.20; H, 3.73; N, 11.96, Found: C, 75.42; H, 3.44; N, 11.58.

Ethyl 2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy] acetate (2): A mixture of compound 1a (3.30g, 0.01mol), ethylbromoacetate (1.20mL, 0.01mol) and anhydrous potassium carbonate (2.10g, 0.015mol) in 50 mL dry acetone was refluxed for 24h. The reaction mixture was cooled and poured onto ice/cold water, the solid that separated out was filtered, dried and recrystallized from ethanol to give compound 2.

Yield 74%, M.P. 110-112°C, IR (KBr) cm^{-1}: 2219 (C≡N), 1752 (C=O, ester). ^{1}H-NMR (DMSO-d_6) δ: 1.13 (t, 3H, $CH_2\underline{CH_3}$), 4.19 (q, 2H, $\underline{CH_2}CH_3$), 5.16 (s, 2H, OCH_2-), 7.45-7.83 (m, 10H, Ar-H, pyridine H5). ^{13}C-NMR (DMSO-d_6) δ: 14.12(CH_3), 60.82(CH_2), 63.79(C_{24}), 93.41(C_{12}), 108.81(C_3), 111.63 (C_{14}), 113.43 (C_7), 114.71 ($C_{18,20}$), 115.91 (C_{22}), 116.20 (C_4), 122.48 (C_5), 124.70 (C_9), 126.83 (C_6), 127.81 ($C_{17,21}$), 131.62 (C_{16}), 148.13 (C_2), 152.61 (C_8), 155.14 (C_{13}), 155.63 (C_{15}), 163.02 (C_{19}), 164.99 (C_{11}), 168.06 (C=O). MS m/z (%): 416 [M^+] (67), 417 [M+1] (33), 343 [M-$COOC_2H_5$] (100). Anal. Calcd. For $C_{24}H_{17}FN_2O_4$ (416.40): C, 69.23; H, 4.12; N, 6.73. Found: C, 69.51; H, 4.22; N, 6.34.

2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy] aceto hydrazide (3): A mixture of compound 2 (4.16g, 0.01mol), hydrazine hydrate (98%) (2 mL, 0.04mol) and 30 mL absolute ethanol was refluxed for 4h. The reaction mixture was cooled; the formed precipitate was filtered, dried and recrystallized from acetic acid to give compound 3.

Yield 80%, M.P. 220-222°C, IR (KBr) cm^{-1}: 3438, 3315, 3236 (NH, NH_2), 2219 (C≡N), 1660 (C=O, amide). ^{1}H-NMR (DMSO-d_6)δ: 4.98 (s, 2H, OCH_2-), 7.43-7.74 (m, 10H, Ar-H, pyridine H5), 8.66 (s, 1H, NH, exchangeable by D_2O), 9.43 (s, 2H, NH_2, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6)δ: 64.50 (C_{24}), 93.21 (C_{12}), 109.50 (C_3), 111.78 (C_{14}), 113.20 (C_7), 114.70 ($C_{18,20}$), 115.91(C_{22}), 116.23 (C_4), 122.44 (C_5), 123.93 (C_9), 126.77 (C_6), 128.04 ($C_{17,21}$), 130.99 (C_{16}), 148.33 (C_2), 152.74 (C_8), 155.21 (C_{13}), 155.61 (C_{15}), 163.28 (C_{19}), 165.92 (C_{11}), 168.00 (CO).MS m/z (%): 402[M^+] (8) 405 [M+3] (24), 343 [M-$CONHNH_2$] (100), 330 [343-CH] (11), 313 [329-O] (37). Anal. Calcd. For $C_{22}H_{15}FN_4O_3$ (402.38): C, 65.67; H, 3.76; N, 13.92. Found: C, 65.33; H, 3.81; N, 13.53.

***2-[(5-Thioxo-1,2,4-oxadiazolin-3-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile(4)*:** Compound 3 (1.61 g, 0.004 mol), was dissolved in a hot solution of (0.23 g, 0.004 mol) potassium hydroxide in 50 mL 96% ethanol, then 30 mL carbon disulphide was added and the reaction mixture was heated in water bath until the evolution of hydrogen sulphide ceased. The excess carbon disulphide evaporated under reduced pressure and the reaction mixture was cooled, treated with (5 mL) acetic acid. The resulting solid was collected by filteration, dried and recrystallized from acetic acid to give compound 4 .

Yield 70%, M.P.: 178-180°c, IR (KBr) cm^{-1}: 3173 (NH), 2223 (C≡N), 1160 (C=S) and disappearance of (C=O, amide). ^{1}H-NMR (DMSO-d_6)δ: 5.69 (s, 2H, OCH_2-), 7.41-7.82 (m, 11H, Ar-H, pyridine H5, NH, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6) δ: 59.17 (C_{24}), 94.40 (C_{12}), 109.94 (C_3), 112.41 (C_{14}), 114.73 (C_7), 115.35 ($C_{8,20}$), 116.59 (C_{22}), 116.88 (C_4), 123.13 (C_5), 124.58 (C_9), 127.46 (C_6), 128.56 ($C_{17,21}$), 131.86 (C_{16}), 148.09 (C_2), 153.29 (C_8), 155.87 (C_{13}), 156.50 (C_{15}), 159.77 (C-*oxadiazol*e), 162.37 (C_{19}), 163.29 (C_{11}), 179.44 (CS). MS m/z (%): 445 [M+1] (18), 333 [M-$C_3H_2N_2OS$] (27), 76 [C_6H_4] (100). Anal. Calcd. For $C_{23}H_{13}FN_4O_3S$ (444.44): C, 62.16; H, 2.93; N, 12.61; S, 7.21. Found: C, 62.31; H, 2.54; N, 12.92; S, 6.91.

2-[(4-Amino-5-thioxo-1,2,4-triazolin-3-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile(5): A mixture of compound 4 (0.45g, 0.001 mol), hydrazine hydrate (98%) (0.20 mL, 0.004 mol) in 10 ml DMF was refluxed for 5h. The reaction mixture was cooled, poured onto ice/cold water, acidified by hydrochloric acid, the formed precipitate was filtered, dried and recrystallized from ethanol to give compound 5.

Yield 65%, M.P. 260-262°C, IR (KBr) cm^{-1}: 3288, 3103 (NH, NH_2), 2219 (C≡N), 1163 (C=S). ^{1}H-NMR (DMSO-d_6) δ: 5.22 (s, 2H, OCH_2-), 7.33-8.15 (m, 11H, Ar-H, pyridine H5, NH, exchangeable by D_2O), 9.11(S, 2H, NH_2, exchangeable by D_2O), ^{13}C-NMR (DMSO-d_6) δ: 58.17 (C24), 93.48 (C12), 109.23 (C3), 111.87 (C14), 114.99 (C7), 115.86 (C18.20), 116.29 (C22), 116.72 (C4), 122.99 (C5), 124.88 (C9), 127.64 (C6), 128.71 (C17.21), 131.91 (C16), 148.39 (C2), 153.44 (C8), 155.91 (C13), 156.62 (C15), 159.88 (C-triazole), 162.47 (C19), 163.30 (C11), 181.53 (CS). MS m/z (%): 456 [M-2] (3), 330 [M-$C_3H_4N_4S$] (100). Anal. Calcd. For $C_{23}H_{15}FN_6O_2S$ (458.46): C, 60.25; H, 3.29; N, 18.33; S, 6.99. Found: C, 60.44; H, 3.51; N, 18.69; S, 7.23.

2-[2-(3-Methyl-1-H-pyrazol-5-one-1-yl)-2-oxoethoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile(6),2-[2-(1H-pyrazol-3,5-dione-1-yl)-2-oxoethoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile(7)and2-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile (8)

General procedure : Refluxing a mixture of compound 3 (0.81g, 0.002 mol), with ethylacetoacetate or diethylmalonate and/or acetyl acetone in 15 mL acetic acid for 8h. The formed precipitate after cooling was filtered, dried and recrystallized from proper solvent to give compounds 6, 7 and 8 respectively.

2-[2-(3-Methyl-1-H-pyrazol-5-one-1-yl)-2-oxoethoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl) pyridine-3-carbonitrile (6): Yield 52%, M.P. 300°C (acetic acid). IR (KBr) cm^{-1}: 2220 (C≡N), 1714 (C=O, cyclic), (C=O, amide). ^{1}H-NMR (DMSO-d_6)δ: 1.95 (s, 3H, CH_3), 2.15 (s, 2H, CH_2 cyclic), 5.08 (s, 2H, OCH_2-), 7.39-7.81 (m, 10H, Ar-H, pyridine H5). ^{13}C-NMR (DMSO-d_6) δ:22.23 (CH_3), 41.12 (CH_2-cyclic), 65.21 (C_{24}), 93.47 (C_{12}), 109.43 (C_3), 111.22 (C_{14}), 113.37 (C_7), 114.40 ($C_{18,20}$), 115.79 (C_{22}), 116.01 (C_4), 122.33 (C_5), 123.79 (C_9), 126.62 (C_6), 128.32 ($C_{17,21}$), 131.14 (C_{16}), 148.28 (C_2), 152.61 (C_8), 153.32 (C-pyrazole), 155.23 (C_{13}), 155.51 (C_{15}), 160.23 (CO-cyclic) 163.26 (C_{19}), 165.95 (C_{11}), 168.05 (CO). MS m/z (%): 468[M^+] not recorded 470 [M+2] (2), 371 [M-$C_4H_5N_2O$] (66), 343 [371-CO] (100). Anal. Calcd. For $C_{26}H_{17}FN_4O_4$ (468.44): C, 66.66; H, 3.66; N, 11.96. Found: C, 66.24; H, 4.11; N, 11.68.

2-[2-(1H-pyrazol-3,5-dione-1-yl)-2-oxoethoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile (7): Yield 70%, M.P. 288-290°C (acetic acid). IR (KBr) cm^{-1}: 3179 (NH), 2220 (C≡N), 1684 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 3.20 (s, 2H, cyclic CH_2), 5.11 (s, 2H, OCH_2-), 7.31-7.88 (m, 10H, Ar-H, pyridine H5), 9.92 (s, 1H, NH, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6) δ: 43.90 (CH_2-cyclic), 64.12 (C_{24}), 93.17 (C_{12}), 109.50 (C_3), 111.70 (C_{14}), 113.05 (C_7), 114.07 ($C_{18.20}$), 115.89 (C_{22}), 116.25 (C_4), 122.42 (C_5), 123.83 (C_9), 126.74 (C_6), 128.02 ($C_{17.21}$), 131.03 (C_{16}), 148.26 (C_2), 152.72 (C_8), 155.16 (C_{13}), 155.48 (C_{15}), 161.68 (CO-cyclic), 163.26 (C_{19}), 164.98 (C_{11}), 165.95 (CO-cyclic), 168.05 (CO). MS m/z (%):442 [M-CO] not recoded 444 [442+2H] (16), 371 [M-$C_3H_3N_2O_2$] (100), 343 [371-CO] (85), 330 [343-CH] (83). Anal. Calcd. For $C_{25}H_{15}FN_4O_5$ (470.41): C, 63.83; H, 3.21; N, 11.91. Found: C, 63.45; H, 3.51; N, 12.13.

2-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pridine-3-carbonitrile (8): Yield 40%, M.P. 228-230°C (acetic acid).. IR (KBr) cm^{-1}: 2220 (C≡N), 1649 (C=O, amide). ^{1}H-NMR (DMSO-d_6)δ: 2.30 (s, 6H, 2(CH_3)), 5.10 (s, 2H, OCH_2-), 7.20-7.83 (m, 11H, Ar-H, pyridine H5, pyrazol H4). ^{13}C-NMR (DMSO-d_6) δ: 14.22 (CH_3), 15.53 (CH_3), 64.99 (C_{24}), 93.31 (C_{12}), 109.50 (C_3), 110.91 (CH-pyrazole), 111.66 (C_{14}), 113.24 (C_7), 114.60 ($C_{18,20}$), 115.83 (C_{22}), 116.16 (C_4), 122.39 (C_5), 123.71 (C_9), 126.54 (C_6), 128.24 ($C_{17,21}$), 130.29 (C_{16}), 140.11 (C-pyrazole), 140.32 (C-pyrazole), 148.41 (C_2), 152.62 (C_8), 155.12 (C_{13}), 155.58 (C_{15}), 163.32 (C_{19}), 165.86(C_{11}), 169.89 (CO). MS m/z (%): 466 [M^+] (14), 467 [M+1] (24), 452 [M-CH_2] (17), 329 [M-$C_7H_9N_2O$] (17), 330 [329+H] (38),

139 [$C_7H_{11}N_2O$] (100). Anal. Calcd. For $C_{27}H_{19}FN_4O_3$ (466.46): C, 69.52; H, 4.11; N, 12.01. Found: C, 69.73; H, 4.34; N, 12.41.

***2-[(5-Mercapto-1H-1,2,4-triazol-3-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile (9)*:** A mixture of compound 3 (2.41g, 0.006 mol) and ammonium thiocyanate (2.28g, 0.03 mol) was fused at 200°C for 30 min. The solid mass was triturated with hot water, cooled and acidified with concentrated hydrochloric acid. The formed precipitate was filtered and recrystallized from ethanol to give compound 9.

Yield 77%, M.P. 288-290°c. IR (KBr) cm^{-1}: 3102 (NH), 2219 (C≡N), disappearance band of (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 5.21 (s, 2H, OCH_2),6.91-8.12 (m, 10H, Ar-H, pyridine H5), 12.75 (s, 1H, NH, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6) δ: 59.15 (C_{24}), 93.55 (C_{12}), 109.73 (C_3), 111.63 (C_{14}), 113.91 (C_7), 114.66 ($C_{18,20}$), 115.51 (C_{22}), 116.61 (C_4), 122.76 (C_5), 124.04 (C_9), 126.46 (C_6), 127.58 ($C_{17,21}$), 131.84 (C_{16}), 145.11 (C-SH),148.65 (C_2), 152.55 (C_8), 153.11 (C-triazole), 154.89 (C_{13}), 155.56 (C_{15}), 162.87 (C_{19}), 163.43 (C_{11}). MS m/z (%): 443 [M^+] (25), 330 [M-$C_3H_3N_3S$] (100). Anal. Calcd. For $C_{23}H_{14}FN_5O_2S$ (443.45): C, 62.29; H, 3.18; N, 15.79. Found: C, 62.42; H, 3.25; N, 16.21; S, 7.56.

***2-[(5-Diethylaminoethylthio-1H-1,2,4-triazol-3-yl) methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl) pyridine-3-carbonitrile (10)*:** A mixture of compound 9 (0.45 g, 0.001 mol) and diethylaminoethylchloride hydrochloride (0.14 g, 0.001 mol) in a solution of 0.2 g NaOH in 20 mL hot ethanol was refluxed for 1h. The reaction mixture was poured onto ice/cold water, acidified by hydrochloric acid, the formed precipitate was filtered, dried and recrystallized from ethanol to give compound 10.

Yield 75%, M.P. 308-310°C.IR (KBr) cm^{-1}: 3160 (NH), 2220 (C≡N). ^{1}H-NMR (DMSO-d_6) δ: 1.52 (t, 6H, 2($CH_2\underline{CH_3}$)), 2.51 (q, 4H, 2($\underline{CH_2}CH_3$)), 3.31 (t, 2H, -$CH_2\underline{CH_2}$N‹), 3.60 (t, 2H, S$\underline{CH_2}CH_2$N‹), 4.90 (s, 2H, OCH_2), 7.39-7.79 (m, 10H, Ar-H, pyridine H5), 13.14 (s, 1H, NH, exchangeable by D_2O).^{13}C-NMR (DMSO-d_6) δ:12.24 ($\underline{CH_3}CH_2$), 28.89 (CH_2-S), 46.18 ($CH_3\underline{CH_2}$-N), 50.51 ($CH_2\underline{CH_2}$N), 59.12 (C_{24}), 93.43 (C_{12}), 109.82 (C_3), 112.77 (C_{14}), 114.75 (C_7), 115.42 ($C_{18,20}$), 116.31 (C_{22}), 116.61 (C_4), 122.54 (C_5), 124.46 (C_9), 127.56 (C_6), 128.68 ($C_{17,21}$), 131.53 (C_{16}), 148.65 (C_2), 153.46 (C_8), 154.23 (C=N, triazole), 155.73 (C_{13}), 156.22 (C_{15}), 157.47 (C-NH, triazole), 162.67 (C_{19}), 163.53 (C_{11}). MS m/z (%):543[M+1] (3), 330 [M-$C_9H_{16}N_4S$] (100). Anal. Calcd. For $C_{29}H_{27}FN_6O_2S$ (542.63): C, 64.19; H, 5.02; N, 15.49. Found: C, 64.39; H, 5.33; N, 15.18; S, 6.22.

***2-[(5-Oxo-5,6-dihydrothiazolo[3,2-b]1,2,4-triazol-2-yl) methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl) pyridine-3-carbonitrile (11)*:** A mixture of compound 9 (0.45 g, 0.001 mol), chloroacetic acid (0.1g, 0.001mol) and anhydrous sodium acetate (0.17g, 0.002 mol) in 10 mL glacial acetic acid and 5 mL acetic anhydride was refluxed for 6h. After cooling, the reaction mixture was poured onto ice/cold water, the formed precipitate was filtered, dried and recrystallized to give compound 11.

Yield 82%, M.P. 218-220°C (ethanol). IR (KBr) cm^{-1}: 2220 (C≡N), 1737 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 4.19 (s, 2H, CH_2), 5.51 (s, 2H, OCH_2), 7.01-7.77 (m, 10H, Ar-H, pyridineH5).^{13}C-NMR(DMSO-d_6) δ: 28.91 (CH_2-cyclic), 58.95 (C_{24}), 93.85 (C_{12}), 108.73 (C_3), 111.59 (C_{14}), 113.75 (C_7), 114.42 ($C_{18,20}$), 115.72 (C_{22}), 116.85 (C_4), 122.62 (C_5), 124.21 (C_9), 127.24 (C_6), 127.56 ($C_{17,21}$), 131.65 (C_{16}), 148.68 (C_2), 152.45 (C_8), 155.24 (C_{13}), 155.92 (C_{15}), 159.57 (C-S), 161.23 (C-N), 163.01 (C_{19}), 164.43 (C_{11}), 189.54 (CO-cyclic). MS m/z (%): 483 [M^+] (4), 440 [M-$COCH_3$], 330 [M-$C_5H_3N_3OS$] (100). Anal. Calcd. For $C_{25}H_{14}FN_5O_3S$ (483.47): C, 62.11; H, 2.92; N, 14.49; S, 6.63. Found: C, 62.42; H, 2.56; N, 14.21; S, 6.87.

2-[(6-Arylidine-5-Oxo-5,6-dihydrothiazolo[3,2-b]1,2,4-triazol-2-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitriles (12a,b)

***General procedure*:** A mixture of compound 9 (0.45g, 0.001mol), chloroacetic acid (0.1g, 0.001mol), anhydrous sodium acetate (0.17g, 0.002mol) and the appropriate aromatic aldehydes, namely, p-anisaldehyde and/or 3,4,5-trimethoxybenzaldehyde (0.001mol) in 10 mL glacial acetic acid and 5 mL acetic anhydride was refluxed for 6h. After cooling, the reaction mixture was poured onto ice/cold water, the formed precipitate was filtered, dried and recrystallized to give compounds 12a,b respectively.

***2-[(6-(p-Methoxybenzylidine)-5-Oxo-5,6-dihydrothiazolo[3,2-b]1,2,4-triazol-2-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile (12a)*:** Yield 51%, M.P. 198-200°C (ethanol). IR (KBr) cm^{-1}: 2220 (C≡N), 1753 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 3.75(s, 3H, OCH_3), 5.09 (s, 2H, OCH_2), 6.94-8.06 (m, 15H, Ar-H, pyridine H5). ^{13}C-NMR (DMSO-d_6) δ: 55.27 (OCH_3), 60.50 (C_{24}), 89.15 (C_{12}), 108.76 (C_3), 111.52 (C_{14}), 113.91 (C_7 and 2C,benzene), 115.79 ($C_{18,20}$), 116.08 (C_{22}), 116.19 (C_4), 121.96 (C_5), 124.78 (C_9), 127.27 (C_6), 127.56 (3C,benzene), 127.99 ($C_{17,21}$), 130.77 (C_{16}), 132.13 (=CH-), 149.09 (C=,cyclic), 148.15 (C_2), 154.36 (C_8), 155.15 (C_{13}), 158.16 (C_{15}), 160.16 (C-S and C-O,benzene), 160,89 (C=N),

161.68 (C_{19}), 164.98 (C_{11}), 178.55 (CO-cyclic). MS m/z (%): 601 [M^+] not recorded 598 [M-3] (2), 569 [M-CH_3OH] (2), 330 [M-$C_{12}H_9N_3O_2S$] (100). Anal. Calcd. For $C_{33}H_{20}FN_5O_4S$ (601.61): C, 65.88; H, 3.35; N, 11.64; S, 5.33. Found: C, 65.57; H, 3.82; N, 11.92; S, 5.66.

***2-[(6-(3,4,5-Trimethoxybenzylidine)-5-Oxo-5,6-dihydrothiazolo[3,2-b]1,2,4-triazol-2-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile (12b)*:** Yield 49%, M.P. 230-232°C (ethanol). IR (KBr) cm^{-1}: 2219 (C≡N), 1742 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.57, 3.88 (s, 9H, 3(OCH_3), 5.11 (s, 2H, OCH_2), 6.94-8.06 (m, 13H, Ar-H, pyridine H5). MS m/z (%): 662[M+1] (5), 330[M-$C_{15}H_{13}N_3O_4S$] (100). Anal. Cald. For $C_{35}H_{24}FN_5O_6S$ (661.66): C, 63.53; H, 3.66; N, 10.58; S, 4.85. Found: C, 63.89; H, 3.92; N, 10.21; S, 5.12.

N-(Substituted benzylidene)-2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluoro phenyl) pyridin-2-yloxy] acetohydrazides (13a, b) and 2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluoro phenyl) pyridin-2-yloxy] N`-[(substituted) methylene] acetohydrazides (13c-e).

***General procedure*:** A mixture of compound 3 (0.81g, 0.002 mol), appropriate aromatic aldehyde, namely, 3,4,5-trimethoxybenzaldehyde, p-chlorobenzaldehyde, 1-naphthaldehyde, thiophene-2-carboxyldehyde and/or indole-3- carboxyldehyde (0.002 mol) in 20 mL ethanol was refluxed for 6h. The formed precipitate after cooling was filtered, dried and recrystallized to give compounds 13a-e respectively.

N-(3,4,5-Trimethoxybenzylidene)-2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]acetohydrazide (13a): Yield 76%, M.P. 210-212°C (acetic acid). IR (KBr) cm^{-1}: 3216 (NH), 2223 (C≡N), 1664 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 3.33, 3.67, 3.81 (s, 9H, 3(OCH_3)), 5.65 (s, 2H, OCH_2-), 6.99-7.83 (m, 13H, Ar-H, CH, pyridine H5), 11.74 (s, 1H, NH, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6)δ: 55.94 (3(OCH_3)), 64.61 (C_{24}), 93.32 (C_{12}), 104.23 (2-CH-benzene), 108.88 (C_3), 111.70 (C_{14}), 113.27 (C_7), 114.55 ($C_{18,20}$), 115.94 (C_{22}), 116.24 (C_4), 122.31 (C_5), 124.22 (C_9), 126.51 (C_6), 127.77 (C_{17}, C_{21} and C-benzene), 130.02 (C_{16}), 140.01 (C-benzene), 141.35 (CH=N), 148.32 (C_2), 149.01 (2C-benzene), 153.21 (C_8), 155.31 (C_{13}), 155.13 (C_{15}), 163.10 (C_{19}), 165.81 (C_{11}), 168.34 (CO), MS m/z (%): 580 [M^+] (23), 581 [M+1] (23), 330 [M-$C_{12}H_{14}N_2O_4$] (77), 50 [C_4H_2] (100). Anal. Calcd. For $C_{32}H_{25}FN_4O_6$ (580.56): C, 66.20; H, 4.34; N, 9.65. Found: C, 66.43; H, 4.72; N, 9.32.

N(4-Chlorobenzylidene)-2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy] acetohydrazide (13b): Yield 84%, M.P. 260-262°C (acetic acid). IR (KBr) cm^{-1}: 3196 (NH), 2220 (C≡N), 1698 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 5.45 (s, 2H, OCH_2-), 7.12-7.93 (m, 15H, Ar-H, CH, pyridine H5), 10.84 (s, 1H, NH, exchangeable by D_2O) MS m/z (%): 524, 526 [M^+] (3.3, 4.1), 371 [M-$C_7H_6N_2Cl$] (17), 343 [371-CO] (38), 330 [343-CH] (81), 89 [C_7H_5] (100). Anal. Calcd. For $C_{25}H_{18}ClFN_4O_3$ (524.93): C, 66.35; H, 3.46; N, 10.67. Found: C, 66.76; H, 3.57; N, 10.34.

2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]-N`-[(naphthalen-1-yl) methylene] acetohydrazide (13c): Yield 83%, M.P.: 280-282°C (acetic acid). IR (KBr) cm^{-1}: 3202 (NH), 2220 (C≡N), 1663 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 5.55 (s, 2H, OCH_2-), 7.10-7.88 (m, 18H, Ar-H, CH, pyridine H5), 11.54 (s, 1H, NH, exchangeable by D_2O). MS m/z (%):540 [M^+] not recorded, 371 [M-$C_{11}H_9N_2$] (16), 343 [371-CO] (42), 330 [343-CH] (67), 197 [$C_{12}H_9N_2O$] (28), 153 [$C_{11}H_7N$] (81), 89 [C_7H_5] (100). Anal. Calcd. For $C_{35}H_{24}FN_4O_3$ (540.54): C, 73.32; H, 3.92; N, 10.36. Found: C, 73.52; H, 4.12; N, 10.61.

2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]-N`-[(thiophen-2-yl) methylene] acetohydrazide (13d): Yield 76%, M.P. 208-210°C (acetic acid). IR (KBr) cm^{-1}: 3207 (NH), 2223 (C≡N), 1662 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 5.64 (s, 2H, OCH_2-), 7.13-7.98 (m, 14H, Ar-H, CH, pyridine H5), 11.24 (s, 1H, NH, exchangeable by D_2O). MS m/z (%): 496 [M^+] (7), 371 [M-$C_5H_5N_2S$] (62), 343 [371-CO] (69), 330 [343-CH] (73), 96 [C_5H_4S] (100). Anal. Calcd. For $C_{27}H_{17}FN_4O_3S$ (496.51): C, 65.31; H, 3.45; N, 11.28; S, 6.46. Found: C, 65.55; H, 3.72; N, 11.44; S, 6.12.

N-[(1H-Indol-3-yl)methylene]-2-[6-(benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy] acetohydrazide (13e): Yield 53%, M.P. 285-286°C (acetic acid). IR (KBr) cm^{-1}: 3415 (NH, indole), 3184 (NH, amide), 2216 (C≡N), 1687 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 5.44 (s, 2H, OCH_2-), 7.11-7.78 (m, 16H, Ar-H, CH, pyridine H5), 11.24 (s, 1H, NH, exchangeable by D_2O). MS m/z (%): 529 [M^+] (29), 330 [M-$C_{11}H_9N_3O$] (33), 130 [C_9H_8N] (71), 63 [C_5H_3] (100). Anal. Calcd. For $C_{31}H_{20}FN_5O_3$ (529.52): C, 70.31; H, 3.81; N, 13.23. Found: C, 70.57; H, 3.61; N, 13.51.

2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]-N-(2,5-dioxopyrrolidin-1-yl) acetamide(14a),2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl)acetamide(14b)and2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluoro phenyl) pyridin-2-yloxy]-N-(1,3-dioxoisoindolin-2-yl) acetamide (14c)

***General procedure*:** A mixture of compound 3 (0.81g, 0.002mol) and the appropriate acid anhydride, namely, succinic anhydride, maleic anhydride and/or phthalic anhydride (0.002mol) in 15 mL acetic acid was refluxed for 8 h. The formed precipitate was filtered, dried and recrystallized to give compounds 14a-c respectively.

***2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]-N-(2,5-dioxopyrrolidin-1-yl) acetamide (14a)*:** Yield 55%, M.P. 238-240°C (acetic acid). IR (KBr) cm^{-1}: 3193 (NH), 2218 (C≡N), 1797, 1735 (2C=O), 1695 (C=O, amide). ^{1}H-NMR (DMSO-d_6): δ 2.78 (s, 4H, 2(CH_2)), 5.25 (s, 2H, OCH_2), 7.30-7.97 (m, 10H, Ar-H, pyridine H5), 9.97 (s, 1H, NH, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6) δ: 26.34 (2CH_2-cyclic), 64.12 (C_{24}), 93.08 (C_{12}), 109.76 (C_3), 111.69 (C_{14}), 113.21 (C_7), 114.91 ($C_{18,20}$), 115.98 (C_{22}), 116.27 (C_4), 122.39 (C_5), 123.89 (C_9), 126.76 (C_6), 128.04 ($C_{17,21}$), 131.11 (C_{16}), 148.30 (C_2), 152.68 (C_8), 155.21 (C_{13}), 155.60 (C_{15}), 163.09 (C_{19}), 164.98 (C_{11}), 168.03 (CO), 174.04 (2CO-cyclic). MS m/z (%): 484 [M^+] (19), 371 [M-$C_4H_5N_2O_2$] (39), 343 [371-CO] (100), 330 [343-CH] (30). Anal. Calcd. For $C_{26}H_{17}FN_4O_5$ (484.44): C, 64.46; H, 3.54; N, 11.57. Found: C, 64.66; H, 3.74; N, 11.72.

2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]-N-(2,5-dioxo-2H-pyrrol-1(5H)-yl) acetamide (14b): Yield 51%, M.P. 242-243°C (acetic acid). IR (KBr) cm^{-1}: 3212 (NH), 2214 (C≡N), 1745 (C=O), 1687 (C=O, amide). ^{1}H-NMR (DMSO-d_6): δ 5.27 (s, 2H, OCH_2) 7.18-7.93(m, 12H, Ar-H, pyridine H5, CH=CH pyrrole ring), 10.94 (s, 1H, NH, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6) δ: 63.89 (C_{24}), 93.17 (C_{12}), 109.61 (C_3), 111.76 (C_{14}), 113.30 (C_7), 114.88 ($C_{18,20}$), 115.99 (C_{22}), 116.28 (C_4), 122.39 (C_5), 124.02 (C_9), 126.78 (C_6), 128.04 ($C_{17,21}$), 131.00 (C_{16}), 133.77 (2CH-cyclic), 148.37 (C_2), 152.70 (C_8), 155.24 (C_{13}), 155.63 (C_{15}), 163.06 (C_{19}), 165.20 (C_{11}), 166.97 (2CO-cyclic), 167.86 (CO). MS m/z (%):482 [M^+] (15), 371 [M-$C_4H_3N_2O_2$] (50), 344 [371-CO] (100).Anal. Calcd. For $C_{26}H_{15}FN_4O_5$ (482.42): C, 64.73; H, 3.13; N, 11.61. Found: C, 64.42; H, 3.23; N, 11.83.

***2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]-N-(1,3-dioxoisoindolin-2-yl) acetamide (14c)*:** Yield 57%, M.P. 240-242°C (acetic acid). IR (KBr) cm^{-1}: 3187 (NH), 2220 (C≡N), 1793, 1744 (2C=O), 1691 (C=O, amide). ^{1}H-NMR (DMSO-d_6): δ 5.29 (s, 2H, OCH_2) 7.18-7.93(m, 14H, Ar-H, pyridine H5), 10.72 (s, 1H, NH, exchangeable by D_2O). MS m/z (%): 532 [M^+] (11), 371 [M-$C_8H_5N_2O_2$] (94), 343 [M-CO] (100). Anal. Calcd. For $C_{30}H_{17}FN_4O_5$ (532.48): C, 67.67; H, 3.22; N, 10.52. Found: C, 67.43; H, 3.44; N, 10.38.

2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]-N`-substituted acetohydrazide (15a-e)

***General procedure*:** A mixture of compound 3 (0.81g, 0.002mol) and the appropriate alkyl halide, namely, benzene sulphonyl chloride, p-toluene sulphonyl chloride, chloro acetone, acetyl chloride and/or benzoyl chloride (0.002mol) in 20 mL ethanol was refluxed for 6 h. The formed precipitate was filtered, dried and recrystallized from proper solvent to give compounds 15a-e respectively.

***2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]-N`-benzenzsulphonyl acetohydrazide (15a)*:** Yield 74%, M.P. 188-190°C (ethanol). IR (KBr) cm^{-1}: broad band centered at 3231 (NH), 2220 (C≡N), 1690 (C=O, amide), 1373, 1166 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 5.21 (s, 2H, OCH_2), 7.23-7.85 (m, 15H, Ar-H, pyridine H5), 8.13 (s, 1H, NH, exchangeable by D_2O), 10.99 (s, 1H, NH, exchangeable by D_2O). MS m/z (%): 544 [M+2] (7), 330 [M-$C_8H_8N_2O_3S$] (34), 54 [C_4H_6] (100). Anal. Calcd. For $C_{28}H_{19}FN_4O_5S$ (542.54): C, 61.99; H, 3.53; N, 10.33; S, 5.91. Found: C, 61.56; H, 3.82; N, 10.54; S, 6.23.

***2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl)pyridin-2-yloxy]-N`-p-toluenesulphonyl acetohydrazide (15b)*:** Yield 60%, M.P. 268-270°C (ethanol). IR (KBr) cm^{-1}: broad band centered at 3226 (NH), 2222 (C≡N), 1692 (C=O, amide), 1369, 1133 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 2.26 (s, 3H, CH_3), 5.24 (s, 2H, OCH_2), 7.43-7.82 (m, 14H, Ar-H, pyridine H5), 8.00 (s, 1H, NH, exchangeable by D_2O), 11.62 (s, 1H, NH, exchangeable by D_2O). ^{13}C-NMR (DMSO-d_6) δ: 20.81 (CH_3), 63.88 (C_{24}), 93.17 (C_12), 109.5 (C_3), 111.70 (C_{14}), 113.4 (C_7), 114.88 ($C_{18,20}$), 115.98 (C_{22}), 116.35 (C_4), 122.54 (C_5), 123.92 (C_9),

125.51 (2C-benzene), 126.88 (C_6), 128.15 (C_{17}, C_{21} and 2C-benzene), 131.05 (C_{16}), 137.85 (C-benzene), 145.45 (C-benzene), 148.33 (C_2), 152.57 (C_8), 155.23 (C_{13}), 155.70 (C_{15}), 163.01 (C_{19}), 165.04 (C_{11}), 166.87 (CO). MS m/z (%): 403 [M-$C_7H_5O_2S$] (2.6), 330 [403-$C_2H_5N_2O$] (100), 155 [$C_7H_7O_2S$] (2). Anal. Calcd. For $C_{29}H_{21}FN_4O_5S$ (556.56): C, 62.58; H, 3.80; N, 10.07; S, 5.76. Found: C, 62.98; H, 3.56; N, 10.42; S, 6.21.

***2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]-N`-(2-oxopropyl) acetohydrazide (15c)*:** Yield 69%, M.P. 228-230°C (methanol). IR (KBr) cm^{-1}: broad band centered at 3209 (NH), 2221 (C≡N), 1720 (C=O), 1687 (C=O, amide). ^{1}H-NMR ($CDCl_3$): δ 1.59 (s, 3H, $COCH_3$), 4.28 (s, 2H, -CH_2-CO), 5.06 (s, 2H, OCH_2), 7.29-7.22 (m, 10H, Ar-H, pyridine H5). MS m/z (%): 443 [M-CH_3] (8), 387 [443-$NHCH_2CO$] (35), 343 [387-$CONH_2$] (67), 330 [343-CH] (100). Anal. Calcd. For $C_{25}H_{19}FN_4O_4$ (458.44): C, 65.50; H, 4.18; N, 12.22. Found: C, 65.91; H, 4.38; N, 12.63.

***2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]-N`-acetylacetohydrazide (15d)*:** Yield 73%, M.P. 288-290°C (methanol). IR (KBr) cm^{-1}: broad bond centered at 3223 (NH), 2224 (C≡N), 1694 (C=O, amide). ^{1}H-NMR (DMSO-d_6): δ 2.30 (s, 3H, $COCH_3$), 5.17 (s, 2H, OCH_2), 7.43-7.82 (m, 10H, Ar-H, pyridine H5), 11.00 (s, 2H, NHNH). MS m/z (%): 444 [M^+] (42), 373 [M-$C_2H_3N_2O$] (50), 165 [$C_{11}H_3NO$] (100). Anal. Calcd. For $C_{24}H_{17}FN_4O_4$ (444.41): C, 64.86; H, 3.86; N, 12.61. Found: C, 64.46; H, 3.52; N, 12.31.

***2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]-N`-benzoylacetohydrazide (15e)*:** Yield 50%, M.P. 299-300°C (methanol). IR (KBr) cm^{-1}: broad band centered at 3223 (NH), 2223 (C≡N), 1693 (C=O, amide). ^{1}H-NMR (DMSO-d_6)δ: 5.21 (s, 2H, OCH_2), 7.13-7.77 (m, 15H, Ar-H, pyridine H5), 10.82 (s, 2H, NHNH, exchangeable by D_2O). MS m/z (%): 509 [M+3] (5), 330 [M-$C_9H_8N_2O_2$] (100). Anal. Calcd. For $C_{29}H_{19}FN_4O_4$ (506.48): C, 68.77; H, 3.78; N, 11.06. Found: C, 68.51; H, 3.42; N, 11.41.

1-[2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]acetyl]-4-substituted thiosemicarbazide (16a-c)

***General procedure*:** A mixture of compound 3 (0.81g, 0.002mol) and the appropriate isothiocyanate, namely, ethylisothiocyanate, cyclohexyl isothiocyanate and/or phenyl isothiocyante in 10 mL DMF was refluxed for 6 h. After cooling pouring onto ice/cold water, acidified by hydrochloric acid, the formed precipitate was filtered, dried and recrystallized from proper solvent to give compounds 16a-c respectively.

***1-[2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]acetyl]-4-ethyl thiosemicarbazide (16a)*:** Yield 80%, M.P. 140-142°C (methanol). IR (KBr) cm^{-1}: 3418, 3227 (NH), 2220 (C≡N), 1697 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 1.31 (t, 3H, $\underline{CH_3}CH_2$), 4.11 (q, 2H, $CH_3\underline{CH_2}$), 5.12 (s, 2H, OCH_2), 7.40-8.00 (m, 10H, ArH, pyridine H5), 8.70, 9.34, 10.21 (s, 3H, 3(NH)), exchangeable by D_2O). ^{3}C-NMR (DMSO-d_6) δ: 14.22 (CH_3), 41.12 (CH_2), 63.65 (C_{24}), 93.28 (C_{12}), 108.53 (C_3), 111.67 (C_{14}), 113.43 (C_7), 114.55 ($C_{18,20}$), 115.83 (C_{22}), 116.18 (C_4), 122.46 (C_5), 124.53 (C_9), 126.58 (C_6), 127.54 ($C_{17,21}$), 131.29 (C_{16}), 148.34 (C_2), 152.63 (C_8), 155.24 (C_{13}), 155.68 (C_{15}), 163.24 (C_{19}), 165.73 (C_{11}), 168.11 (CO), 178.68 (CS). MS m/z (%): 465 [M-C_2H_2+2] (100), 466 [465+1] (33). Anal. Calcd. For $C_{25}H_{20}FN_5O_3S$ (489.52): C, 61.34; H, 4.12; N, 14.31; S, 6.55. Found: C, 61.54; H, 4.33; N, 14.64; S, 6.89.

***1-[2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]acetyl]-4-cyclohexyl thiosemicarbazide (16b)*:** Yield 77%, M.P.: 109-110°C (methanol). IR (KBr) cm^{-1}: 3318, 3256 (NH), 2223 (C≡N), 1679 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 1.17-1.67 (m, 10H, cyclohexyl), 2.40 (m, 1H, CH-cyclohexyl), 5.16 (s, 2H, OCH_2), 7.42-7.80 (m, 10H, Ar-H, pyridine H5), 9.00, 9.28, 10.10 (s, 3H, 3(NH), exchangeable by D_2O). MS m/z (%): 543[M^+](30), 330[M-$C_9H_{15}N_3OS$] (100). Anal. Calcd. For $C_{29}H_{26}FN_5O_3S$ (543.61): C, 64.07; H, 4.82; N, 12.88; S, 5.90. Found: C, 64.35; H, 4.63; N, 12.54; S, 6.21.

***1-[2-[6-(Benzofuran-2-yl)-3-cyano-4-(4-fluorophenyl) pyridin-2-yloxy]acetyl]-4-phenyl thiosemicarbazide (16c)*:** Yield 72%, M.P. 89-90°C (ethanol). IR (KBr) cm^{-1}: 3330, 3265 (NH), 2223 (C≡N), 1680 (C=O, amide). ^{1}H-NMR (DMSO-d_6) δ: 5.21 (s, 2H, OCH_2), 7.22-7.85 (m, 15H, Ar-H, pyridine H5), 9.10, 9.38, 10.22 (s, 3H, 3(NH), exchangeable by D_2O). MS m/z (%): 537[M^+](100). Anal. Calcd. For $C_{29}H_{20}FN_5O_3S$ (537.56): C, 64.79; H, 3.75; N, 13.03; S, 5.96. Found: C, 64.53; H, 4.02; N, 13.41; S, 5.55.

2-[(4-Substituted-5-thioxo-1,2,4-triazolin-3-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitriles(17a-c)

***General procedure*:** Compounds 16a-c (0.001 mol) dissolved in 20 mL ethanolic sodium hydroxid solution (5%) was refluxed for 8h.The reaction mixture was cooled, poured onto ice/cold water, acidified by

hydrochloric acid. The formed precipitate was filtered, dried and recrystallized to give compounds 17a-c

***2-[(4-Ethyl-5-thioxo-1,2,4-triazolin-3-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile(17a)*:** Yield 63%, M.P. 280°C (ethanol). IR (Kbr) cm^{-1}: 3152 (NH), 2223 (C≡N). ^{1}H-NMR (DMSO-d_6) δ: 1.17 (t, 3H, $CH_2\underline{CH_3}$), 4.10 (q, 2H, CH_2CH_3),4.50 (s, 2H, OCH_2) 6.97-7.97 (m, 10H, Ar-H, pyridine H5). ^{3}C-NMR (DMSO-d_6) δ: 13.22 (CH_3), 41.32 (CH_2), 62.12 (C_{24}), 94.28 (C_{12}), 109.51 (C_3), 111.75 (C_{14}), 113.51 (C_7), 114.61 ($C_{18,20}$), 115.90 (C_{22}), 116.22 (C_4), 122.61 (C_5), 124.62 (C_9), 126.72 (C_6), 127.43 ($C_{17,21}$), 131.23 (C_{16}), 148.23 (C_2), 152.66 (C_8), 153.22 (C-triazole), 155.15 (C_{13}), 155.55 (C_{15}), 163.15 (C_{19}), 164.73 (C_{11}), 175.84 (CS). MS m/z (%): 470[M-1] (10), 331 [M-$C_5H_6N_3S$] (71), 57 [C_4H_9] (100). Anal. Calcd. For $C_{25}H_{18}FN_5O_2S$ (471.51): C, 63.68; H, 3.85; N, 14.85; S, 6.80, Found: C, 63.24; H, 3.63; N 14.93; S, 6.52.

***2-[(4-Cyclohexyl-5-thioxo-1,2,4-triazolin-3-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile(17b)*:** Yield 60%, M.P. 310°C (ethanol). IR (KBr) cm^{-1}: 3141 (NH), 2226 (C≡N). MS m/z (%): 525[M^+] (23) 330[M-$C_9H_{13}N_3S$] (100). Anal. Calcd. For $C_{29}H_{24}FN_5O_2S$ (525.60): C, 66.27; H, 4.60; N, 13.32; S, 6.10, Found: C, 66.34; H, 4.32; N, 13.62; S, 6.41.

***2-[(4-Phenyl-5-thioxo-1,2,4-triazolin-3-yl)methoxy]-6-(benzofuran-2-yl)-4-(4-fluorophenyl)pyridine-3-carbonitrile(17c)*:** Yield 57%, M.P. 190°C (ethanol). IR (KBr) cm^{-1}: 3133 (NH), 2220 (C≡N).

MS m/z (%): 503 [M-NH_2] (15), 344 [M-$C_8H_5N_3S$] (68), 330 [M-$C_9H_7N_3S$] (100).Anal. Calcd. For $C_{29}H_{18}FN_5O_2S$ (519.55): C, 67.04; H, 3.49; N, 13.48; S, 6.17, Found: C, 67.38; H, 3.15; N, 13.66; S, 6.29.

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