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SYNTHESIS OF BACTERICIDES *VIA* CARBON NUCLEOPHILIC ADDITION ON 1,3-DIARYLPROP-2-ENONES AS MICHAEL ACCEPTORS

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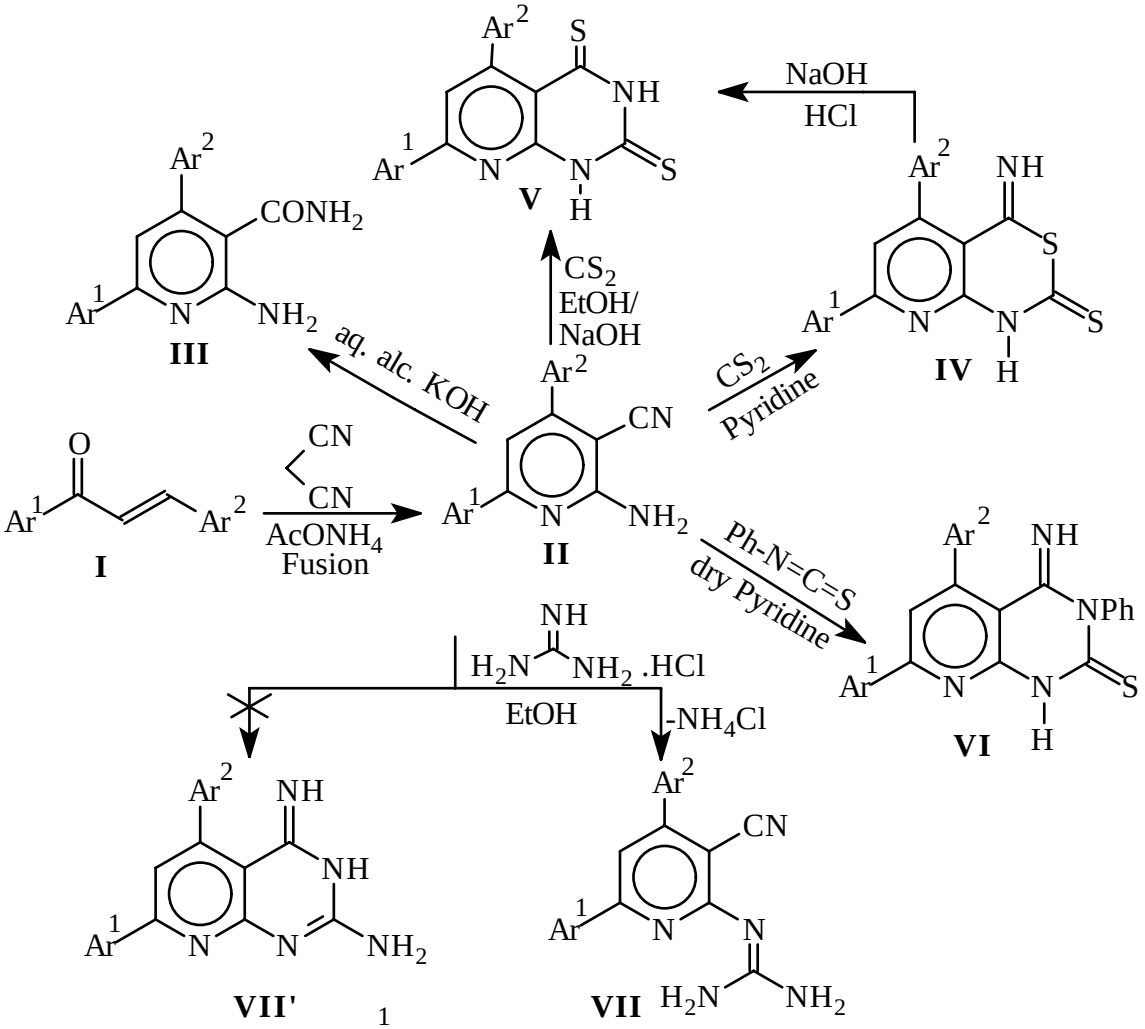
Abstract - Treatment of α,β–unsaturated ketones (**I**) with malononitrile in presence of ammonium acetate afforded 2-amino-4,6-diarylnicotinonitriles (**II**) which reacted with aq. alc. KOH, CS_2 (pyridine), CS_2 (EtOH/NaOH), phenyl isothiocyanate and guanidine hydrochloride to yield the corresponding heterocyclic products (**III-VII**) respectively. When **I** was allowed to react with cyanoacetanilide, ethyl chloroacetate, benzyl cyanide, 4-chlorobenzaldehyde and potassium cyanide, it gave the Michael adducts (**VIII-XII**). Fusion of **XIb** with hydrazine hydrate afforded **XIII** whereas treatment of **XIb** with hydrazine hydrate and/or hydroxylamine hydrochloride gave **XIVa** and **b** respectively. The evaluation of the minimal inhibitory concentration (MIC) of some of the synthesized compounds was carried out.

As an extension of our program to study the addition reactions on α,β-unsaturated aromatic ketones (chalcones)[1-4] as one of the most important classes of conjugate acceptors, we describe in this work one-step and efficient routes which constitute convenient syntheses of heterocyclic compounds (some of which have biological activities) from the above mentioned readily obtainable chalcones. Thus, when 1-(2,4-dimethoxyphenyl)-3-(4'-chlorophenyl)- and/or 3-(3',4'-methylenedioxyphenyl)prop-2-enone (**Ia** and/or **Ib**) was allowed to react with malononitrile in a 1:1 molar ratio in the presence of excess $AcONH_4$, it yielded 2-amino-4,6-diarylnicotinonitriles (**IIa** and **b**) respectively.[5] When the nicotinonitriles (**IIa** and/or **IIb**) were subjected to heating with aq. ethanolic 20% potassium hydroxide, hydrolysis of the cyano functionality occurred to afford 2-amino-4,6-diarylnicotinamides (**IIIa** and **b**) respectively. The reaction of nicotinonitriles (**IIa** and **b**) with carbon disulfide afforded a product depending upon the reaction conditions and permits the synthesis of some new fused thiazines and pyrimidine-2,4-dithiones. When the reaction was carried in refluxing pyridine, the isolated products were identified as 1H-5-aryl-7-(2,4-dimethoxy-phenyl)-4-iminopyrido[2,3-d]thiazine-2-thione derivatives (**IVa**,**b**) respectively. On the other hand, when

compound (**IIa**) was allowed to react with carbon disulfide in refluxing ethanol in the presence of sodium hydroxide followed by acidification with 20% HCl, 1H,3H-5-(4'-chlorophenyl)-7-(2,4-dimethoxyphenyl)-pyrido[2,3-d]pyrimidine-2,4-dithione (**V**) was obtained.[6,7] This reaction represents the synthetic method of choice to synthesise the pyrimidinedithiones. A heterocylic ring transformation was observed when the thiazinthione (**IVa**) was boiled with aq. ethanolic 20% sodium hydroxide solution followed by acidification with 20% HCl since it isomerized to pyrimidinedithione (**V**) which was identified by mp, mixed mp, IR spectra and TLC comparison. Treatment of 2-aminonicotinonitriles (**IIa** and/or **IIb**) with phenyl isothiocyanate and/or guanidine hydrochloride in refluxing dry pyridine and absolute ethanol in the presence of sodium acetate respectively resulted in the corresponding pyrido[2,3-d]pyrimidine-2-thiones (**VIa** and **b**) and 2-guanidopyridine derivatives (**VIIa** and **b**), unfortunately we did not obtain the desired product, pyrido[2,3-d]pyrimidine derivative (**VII'**), which assumed to be formed *via* the cycloaddition of amino group to the cyanide group. Authentic samples of the latter products were also obtained by treatment of **IIa** and **b** with urea and/or thiourea in refluxing ethanol (Scheme 1).

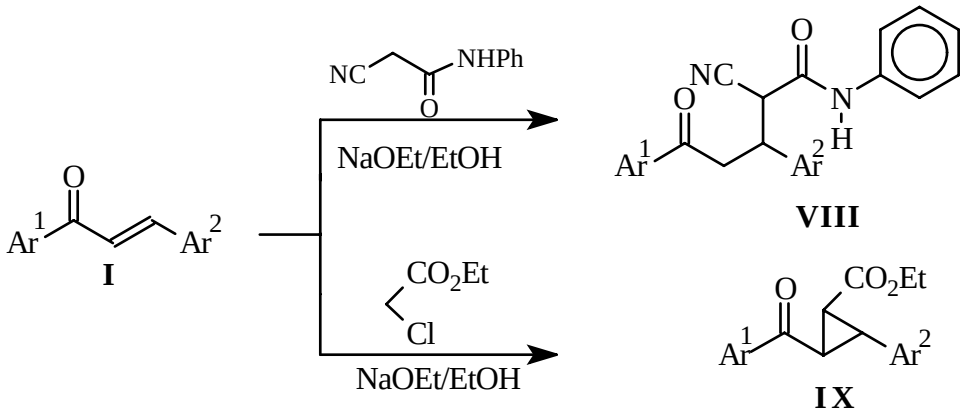


$Ar^1 = C_6H_3(OMe)$-2,4

a, $Ar^2 = C_6H_4Cl$-4 b, $Ar^2 = C_6H_3(O_2CH_2)$-3,4

Scheme 1

Cyanoacetanilide is a typical active methylene-containing compound, so when it was allowed to react with α,β-ethylenic ketones (**Ia** and **b**) in the presence of ethanolic sodium ethoxide as a basic catalyst, the product was identified to be the normal Michael's adducts (**VIIIa** and **b**). The addition of ethyl chloroacetate to α,β-ethylenic ketones could provide a simple synthesis of cyclopropyl derivatives.[8] Thus when **Ia** was treated with ethyl chloroacetate in the presence of sodium ethoxide, it yielded ethyl cyclopropylcarboxylate derivative (**IX**) (Scheme 2).



$Ar^1 = C_6H_3(OMe)\text{-}2,4$

a, $Ar^2 = C_6H_4Cl\text{-}4$ b, $Ar^2 = C_6H_3(O_2CH_2)\text{-}3,4$

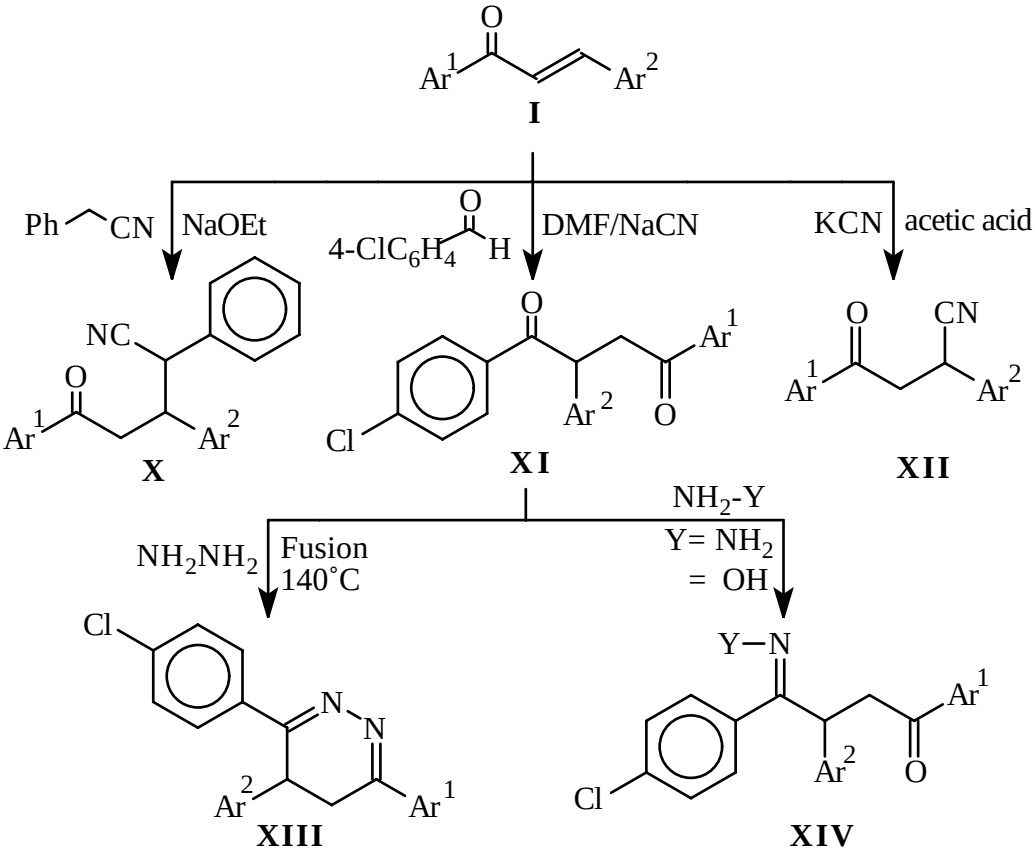
Scheme 2

Base catalyzed conjugate addition of benzyl cyanide[9] to the target compound (**Ib**) gave also the normal adduct (**X**). Stetter[10] has developed an important process for the addition of aldehydes to conjugate acceptors. This process depends upon the in situ generation of a π-stabilized carbanion produced by the addition of a nucleophlic catalyst to the aldehydic carbonyl group. The process is analogous to the benzoin reaction in that it uses a cyanide ion as the catalyst. However, the benzoin reaction is carried out in protic media e.g., ethanol and all steps are reversible, whereas Stetter's process uses cyanide ion in aprotic media e.g., dimethylformamide and the last step is irreversible. Thus, the α,β-unsaturated carbonyl compounds (**Ia**) and/or (**Ib**) were stirred with 4-chlorobenzaldehyde in DMF in the presence of a catalytic amount of sodium cyanide to afford the 1,4-diketones (**XIa** and **b**) respectively.

There is no problem with respect to β-substitution on conjugate hydrocyanation for α,β-ethylenic ketones. So, hydrocyanation of **Ia** was readily carried out by treatment with ethanolic potassium cyanide solution in the presence of few drops of acetic acid at room temperature[11] to give the corresponding nitrile (**XII**). On the other hand, fusion of the 1,4-diketone (**XIb**) with 80% hydrazine hydrate at 140-145˚C resulted in the respective pyridazine derivative (**XIII**) whereas refluxing of **XIb** with 80% hydrazine hydrate in ethanol and/or hydroxylamine hydrochloride in pyridine gave the hydrazone and/or oxime (**XIVa** and **b**) respectively (Scheme 3).

The monohydrazone and monoxime are formed rather than the dihydrazone or dixime could be due to : 1-The polar effect which played a significant role in this reaction, thus p-chlorobenzoyl moiety reacts with nitrogen nucleophiles more rapidly and easily than that of 2,4-dimethoxybenzoyl moiety because the inductive polar effect of the chlorine atom activates the carbonyl group of its own moiety while 2,4-dimethoxybenzoyl moiety stabilizes the enol form than its keto form due to its mesomeric effect.

2- The steric factor of the two -OMe which have some sort of steric hindrance that inhibits the approach of the nitrogen nucleophile.



$Ar^1 = C_6H_3(OMe)\text{-}2,4$

a, $Ar^2 = C_6H_4Cl\text{-}4$ b, $Ar^2 = C_6H_3(O_2CH_2)\text{-}3,4$

Scheme 3

ANTIBACTERIAL EVALUATION OF SOME SELECTIVE SYNTHESIZED COMPOUNDS:

The minimal inhibitory concentration (MIC) of these compounds was determined by the standard broth dilution method (NCCLS, 1993).[12] This experiment was performed using test bacterial organisms belonging to Gram-negative and Gram-positive groups *E. coli* and *S. aureus* respectively, serial dilution of each derivative was prepared ranging from 1 to 128 μg/mL. The bacterial inoculum used was $5x10^5$ Cfu/mL (Cfu = colony forming unit) approximately. The MIC was recorded for each compound as lowest

concentration that inhibits the growth of the test bacterial organism as shown in table (2) which shows that compound (**VIIb**) was the most effective against both Gram-negative and Gram-positive bacterial strains where MIC was 4 and 2 μg/mL respectively followed by compound (**IIIb**) which affects on the tested bacteria at 4 μg/mL and 8 μg/mL level. While the other compounds have moderate effect on the tested bacteria. It may be safely said that compounds (**VIIb** and **IIIb**) can be used as antibacterial agents against both Gram-negative and Gram-positive bacteria.

CONCLUSION

In conclusion, Michael addition reaction of α,β-unsaturated carbonyl compounds (as Michael acceptor) with carbon nucleophiles followed by reaction of nitrogen nucleophiles provides an easy route for the preparation of new heterocyclic compounds depending on the nature of Michael donor and the reaction conditions. From MIC evaluation we can conclude that the most effective tested compounds were **IIIb** and **VIIb** which can be used as bactericides againest both Gram-negative and Gram-positive bacteria.

EXPERIMENTAL

Melting points reported are uncorrected. All IR spectra were recorded on a Pye-Unicam SP 1200 Spectrophotometer using KBr Wafer technique.[13] All ^{1}H-NMR spectra and ^{13}C- NMR were determined on AC-250 (200 MHz.) Bruker.[14-16] In all NMR experiments the internal standard was TMS. All chemical shifts are in ppm downfield from TMS .The MS spectra were determined using MS-TSQ 70 Finnigan MAT and GCMS-QP1000 EX Shimadzu, Japan , EI = 70 ev. Compounds (**Ia** and **b**) were prepared according to the method described.[17]

Ia ,IR [cm^{-1}]: C=C(1615), C=O(1665), C-H aliph. (2964), C-H arom. (3095); ^{1}H-NMR ($CDCl_3$): 3.80 and 3.90 (two s, 6H , 2 OMe), 6.40 and 6.50 (two d, 2H, J = 3.08 Hz, C_3-H and C_5-H respectively in 2,4-dimethoxyphenyl group), 7.30-7.60 (m, 6H, arom. of 4-chlorephenyl group and the two olefinic) and 7.80 (d, 1H, J=9.40 Hz, C_6-H in 2,4-dimethoxyphenyl group).

Ib , IR [cm^{-1}]: C=C (1610), C=O (1660), C-H aliph. (2426), C-H arom. (3080); ^{1}H-NMR ($CDCl_3$) : 3.80 and 3.90 (two s, 6H, 2 OMe), 5.90 (s, 2H, O-CH_2-O), 6.50 and 6.60 (two d, 2H, J = 3.10 Hz, C_3-H, and C_5-H), 7.30-7.70 (m, 5H, arom. and the two olefinic) and 7.80 (d, 1H, J = 9.10 Hz, C_6-H).

Reaction of Malononitrile with 1,3-Diarylprop-2-en-1-ones (Ia and b) ; Formation of 2-Amino-4,6-diarylnicotinonitriles (IIa and b). 1,3-Diarylprop-2-en-1-ones (**Ia** and/or **Ib**) (3.03 g and/or 3.12 g, 0.01 mol) was added to malononitrile (0.80 g, 0.012 mol) in the presence of ammonium acetate (2.31 g, 0.03 mol). The reaction mixture was fused at 140-150 °C for 4 h, cooled, washed with water several times and filtered off, the solid was collected, dried and then recrystallized from suitable solvent to give **IIa** and **b** respectively (cf.Table 1).

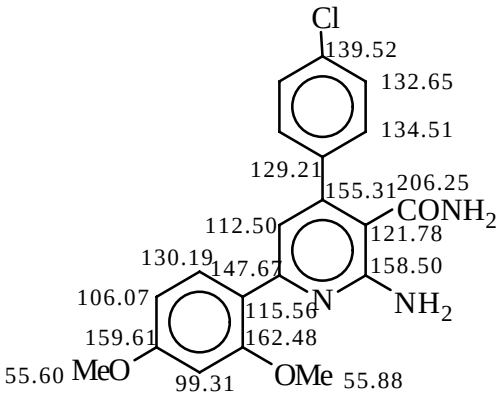
IIa , IR [cm^{-1}]: C=C (1590), C=N (1610), C≡N (2205), C-H aliph. (2920), C-H arom. (3005), NH_2

(3378, 3380, 3475); ^{1}H-NMR (acetone-d_6): 2.92 (s, 2H, NH_2), 3.87 and 3.90 (two s, 6H, 2 OMe), 6.63 and 6.66 (two d, 2H, J = 3.0 Hz, C_3-H and C_5-H), 7.45 (s, 1H, pyridine ring), 7.53-7.75 (m, 4H, arom.) and 7.90 (d, 1H, J = 9.30 Hz, C_6-H); MS, m/z (relative intensity): 365.8, [$M^{+\bullet}$] (20), 367.8, [M+2] (7), 330.3 (5.7), 289.2 (5.7), 253.9 (15), 230 (16.4), 164.9 (100), 137.9 (4.3), 122.9 (10), 120.9 (21.4) and 77 (7.8).

IIb , IR [cm^{-1}]: C=C (1600), C=N (1630), C≡N (2210), C-H aliph. (2980), C-H arom. (3010), NH_2 (3380, 3382, 3490); ^{1}H-NMR (acetone-d_6) : 3.45 (s, 6H, 2 OMe),3.85 (br s, 2H, NH_2), 6.35 (s, 2H, O-CH_2-O), 7.20 (s, 1H, pyridine ring) and 7.75-8.40 (m, 6H, aromatic protons).

Reaction of 2-Amino-4,6-diarylnicotinonitriles (IIa and b) with Potassium Hydroxide ; Formation of 2-Amino-4,6-diarylnicotinamides (IIIa and b). A solution of 20% aqueous ethanolic potassium hydroxide (20 mL) was added to an ethanolic solution of **IIa** and/or **IIb** (0.01 mol in 20 mL of ethanol) and the reaction mixture was heated under reflux with stirring for 5 h , left to cool and neutralized by 10% HCl / ice, then the solid that separated out was washed with water several times, dried, and recrystallized from the proper solvent giving the corresponding nicotinamides (**IIIa** and **b**) respectively.

IIIa , IR [cm^{-1}] : C=C (1595), C=N (1610) , C=O (amide, 1682) , C-H aliph. (2935) C-H arom. (3020) , NH_2 (3380,3465) ; ^{1}H-NMR (acetone-d_6): 2.99(br , 2H, N=CH-NH_2) 3.84 and 3.86 (two s, 6H, 2 OMe), 5.16 (br, 2H, $CONH_2$), 6.60 and 6.64 (two d, 2H, J = 3.1 Hz, C_3-H and C_5-H), 7.23 (s, 1H, pyridine ring), 7.45-7.60 (m, 4H, arom.), 7.85 (d, 1H, J = 9.1 Hz, C_6-H); MS ; m/z (relative intensity): 383.1 [$M^{+\bullet}$], (100), the [M+2] peak with intensity 1/3 of that of the parent peak is also observed, 352 (24.3), 337 (15) , 309 (14.3), 246 (23.6), 231 (17.1), 220 (2.1), 203 (7.1), 164 (11.4), 148 (32.9), 138 (11.4), 121 (12.1); ^{13}C-NMR spectrum exhibited the following signals as follows: -



^{13}C-NMR of compound (IIIa)

IIIb , IR [cm^{-1}]: C=C(1600), C=N(1611), C=O (amide, 1685), C-H aliph. (2922), C-H arom. (3010), NH_2 (3385, 3470); ^{1}H-NMR (acetone-d_6): 3.35 (s, 6H, 2 OMe), 3.80 (s, 2H, NH_2), 5.35 (br s, 2H, $CONH_2$), 6.45 (s, 2H, O-CH_2-O), 7.35 (s, 1H, pyridine ring) and 7.65-8.80 (m, 6H, aromatic protons).

Reaction of 2-Amino-4,6-diarylnicotinonitriles (IIa and b) with Carbon Disulfide in Pyridine ; Formation of 1H-5-Substituted 7-(2,4-Dimethoxyphenyl)-4-iminopyrido[2,3-d]thiazine-2-thione (IVa and b). A mixture of 2-amino-4,6-diarylnicotinonitriles (**IIa** and/or **IIb**) (0.01 mol) and carbon disulfide (10 mL) in pyridine (20 mL) was heated under reflux for 6 h. The solid products that separated out after cooling were acidified with 20% hydrochloric acid, washed with water several times, dried, and then recrystallized from the suitable solvent to give the products (**IVa** and **b**) respectively .

IVa , IR [cm^{-1}]: N-CS-S (1030), C=S (1252), C=C (1607), C=N (1650), SH (2340), C-H aliph. (2926), C-H arom. (3005), NH (3380); ^{1}H-NMR ($CDCl_3$): 1.25 (s, 1H, SH), 1.60 (br , 1H, NH imino), 3.75 and 3.86 (two s, 6H, 2 OMe), 6.55 and 6.65 (two d, 2H, J = 3.1 Hz, C_3-H and C_5-H), 7.25 (s, 1H, pyridine ring), 7.34-7.54 (m, 4H, arom.) and 7.85 (d, 1H, J = 9.1 Hz, C_6-H). The signal for NH-C=S is not observed because it is out of scale which was mesured up to 9.00 ppm; MS, m/z (relative intensity): 441.5 [$M^{+\bullet}$], (2.8), 443.5 [M+2], (10.8), 417.1, (30), 365 (87.8), 354 (10.1), 351(100), 324(7.8), 321(13.5), 305(8.6), 273 (5.7), 259 (6.4), 246(15.7), 244 (15.6), 199 (17.8), 181(18.5), 153.5 (19.3), 125.5 (19.3), 94 (42.8) and 65 (27).

IVb , IR [cm^{-1}]: N-CS-S (1040), C=S(1270), C=C (1615), C=N (1660), SH(2380), C-H aliph. (2930), C-H arom. (3015), NH (3420) ; ^{1}H-NMR (acetone-d_6): 1.46 (s, 1H, SH), 1.76 (br s, 1H, NH imino), 3.48 (s, 6H, 2 OMe), 6.48 (s, 2H, O-CH_2-O), 7.15 (s, 1H, pyridine ring) and 7.80-8.60 (m, 6H, aromatic protons).

Reaction of 2-Amino-4,6-diarylnicotinonitrile (IIa) with Carbon Disulfide in the Presence of Ethanolic NaOH ; Formation of 1H,3H-5-(4-Chlorophenyl)-7-(2,4-dimethoxyphenyl)-pyrido[2,3-d]pyrimidine-2,4-dithione (V). A mixture of 2-amino-4,6-diarylnicotinonitriles **(IIa)** (3.00 g, 0.01 mol) , carbon disulfide (10 mL) and 10% ethanolic sodium hydroxide (30 mL) was heated under reflux for 1 h. The solid product that separated out after cooling was acidified with 20% hydrochloric acid, filtered off , washed with water several times, dried, and then recrystallized from the suitable solvent to afford the product (**V**).

V , IR [cm^{-1}]: C=S (1252 and 1213) , C=C (1607) C-H aliph. (2918 and 2853), C-H arom. (3188), NH (br centered at 3335); ^{1}H-NMR (acetone-d_6): 3.30 (s, 6H, 2 OMe), 7.15, 7.28 (two br s, 2H, 2 -NH), and 7.90-8.50 (m, 8H, aromatic protons); MS , m/z (relative intensity) : 441.5 [$M^{+\bullet}$] (8.1), 443 $[M+2]^{+\bullet}$ (4.1), 371.5 (10.1), 345 (83.2), 331 (100), 324.5 (11.3), 318 (15.4), 302 (6.8), 271 (9.4), 257 (6.4), 244 (18.7), 242.1 (22.7), 197 (17.1), 181 (28.3), 153.5 (19.0), 150.5 (72.2), 125 (29.3), 94 (42.0), 90 (27.5) and 65 (37.4).

Isomerization of IVa into V : A mixture of **IVa** (2.2 g, 0.005 mol) and 10% ethanolic sodium hydroxide (40 mL) was heated under reflux with stirring for 1 h , the solid that separeted out after cooling and acidification with 20% hydrochloric acid was filtered off , washed with water several times , dried and

crystallized from methanol to give a product which was identified (by mp , mixed mp , IR and TLC comparison) to be **V**.

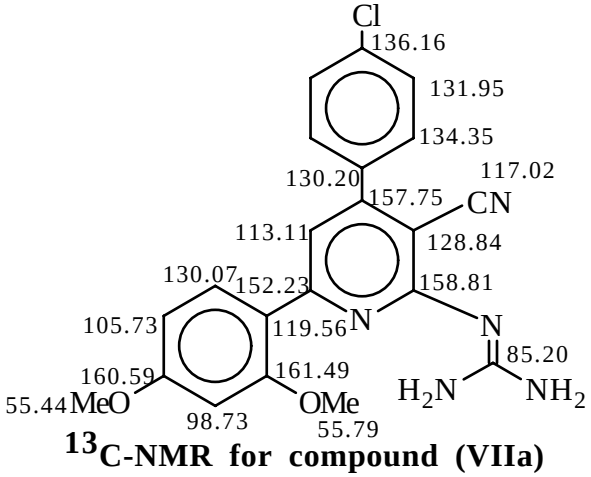
Reaction of 2-Amino-4,6-diarylnicotinonitriles (IIa and b) with Phenyl Isothiocynate; Formation of 1H,3H-5-,7-Diaryl-4-imino-3-phenylpyrido[2,3-d]pyrimidine-2-thione (VIa and b). A solution of phenyl isothiocynate (0.20 g, 0.015 mol) in 10 mL of dry pyridine was added dropwise with stirring , at rt within 15 min, to a solution of **IIa** and/or **IIb** (0.01 mol) in 20 mL of dry pyridine. The reaction mixture was heated under reflux with stirring for 3 h , cooled and poured into 20% HCl/ ice, the solid product was filtered off, washed with water several times, dried and then reccrystallized from the suitable solvent to afford the products (**VIa** and/or **VIb**) respectively .

VIa , IR [cm^{-1}]: N-CS-N (1270), C=C(1610), C=N(1632), C-H aliph. (2980), C-H arom. (3020), NH (3033, 3207) ; MS , m/z (relative intensity): 287.2 [$M^{+\bullet}$] (22.49), 194 (100), 138 (2.71), 93.1 (88), 77(37.1), 64.9 (81), 51.1(14).

VIb , IR [cm^{-1}]: N-CS-N(1280), C=C (1607), C=N (1640), C-H aliph. (2990), C-H arom. (3038), NH (3025, 3200) ; ^{1}H-NMR (acetone-d_6): 1.52 (s, 1H, SH), 1.85 (br s, 1H, NH imino), 3.35 (s, 6H, 2 -OMe), 6.28 (s, 2H, O-CH_2-O), 7.20 (s, 1H, pyridine ring) and 7.55-8.76 (m, 6H, aromatic protons).

Reaction of 2-Amino-4,6-diarylnicotinonitriles (IIa and b) with Guanidine Hydrochloride; Formation of 3-Cyano-4,6-diaryl-2-guanidopyridines (VIIa and b). A mixture of **IIa** and/or **IIb** (0.01 mol) and guanidine hydrochloride (0.012 mol , 0.70 g) in ethanol (30 mL), containing 1.00 g of sodium acetate ,was heated under reflux for 6 h , most of the solvent was removed and then the cold solution was diluted with water. The solid that precipitated was filtered off, washed with water, dried, and then recrystallized from the proper solvent to yield **VIIa** and **b** respectively .

VIIa , IR [cm^{-1}]: C=C (1590), C=N (1611), C≡N(2205), C-H aliph. (2922), C-H arom. (3005), NH_2 (3381, 3420); ^{1}H-NMR (acetone-d_6): 2.90 (s, 4H, two NH_2 groups), 3.87 and 3.89 (two s, 6H, 2 OMe), 6.64 and 6.67 (two d, 2H, J = 3.60 Hz, C_3-H and C_5-H), 7.45 (s, 1H, pyridine ring), 7.57-7.70 (m, 4H, arom.), 7.95 (d, 1H, J = 9.10 Hz, C_6-H); ^{13}C-NMR spectrum exhibited the following signals as follows: -



^{13}C-NMR for compound (VIIa)

MS , m/z (relative intensity): 407.8 [$M^{+\bullet}$] (0.4), 364.2 (44.2), 365.3 (56.4), 296 (1.9), 292 (7.1), 268 (2.1), 254 (15.7), 230 (17.1), 137 (9.2), 111.1 (30.7), 97.2 (46.5), 85.0 (57.2), 70.9 (82.2) and 56.9 (100).

VIIb , IR [cm^{-1}]: C=C (1595), C=N (1620), C≡N(2205), C-H aliph. (2930), C-H arom. (3010), NH_2 (3387, 3472); ^{1}H-NMR ($CDCl_3$): 2.78 (br s, 4H, two NH_2), 3.47 (s, 6H, 2 -OMe), 6.42 (s, 2H, O-CH_2-O) and 7.95-8.80 (m, 7H, aromatic protons); MS , m/z (relative intensity) : 417.2 [$M^{+\bullet}$] (14.27), 375 (58.4), 296 (11.9), 292 (19.3), 263 (22.7), 239 (100), 137 (14.4), 124 (12.3), 121 (42.1), 109 (14.8), 104 (63.2), 94 (23.6), 77 (18.4) and 65 (47.1).

Authentic Samples of VIIa and VIIb. A mixture of **IIa** and/or **IIb** (0.01 mol) and urea or thiourea (0.012 mol) in ethanol (30 mL) was heated under reflux for 6 h , most of the solvent was distilled off and then the cold solution was diluted with water. The solid that precipitated was filtered off, washed with water, dried, and then recrystallized from the proper solvent to yield **VIIa** and **b** respectively .

Reaction of Cyanoacetanilide with 1,3-Diarylprop-2-enones (Ia and b); Formation of 3-Aryl-5-(2,4-dimethoxyphenyl)-2-(N-phenylcarbamido)-5-oxopentanocarbonitrile (VIIIa and b). A solution of 1,3-diarylprop-2-enone (**Ia** and/or **b**) (0.01 mol) in 20 mL of ethanol was added to an ethanolic mixture of cyanoacetanilide (1.9 g , 0.01 mol) and sodium ethoxide (0.23 g. of sodium metal in 10 mL of absolute ethanol). The reaction mixture was heated under reflux with stirring for 3 h, cooled, poured into 20% HCl/ice and filtered off. The solid that separated out was washed with water several times, dried and then recrystallized from the suitable solvent to give the products (**VIIIa** and/or **b**) respectively.

VIIIa , IR [cm^{-1}]: C=O (arom. ketone, 1660), C=O (secondary amide, 1690), C≡N (2210), C-H aliph. (2900), C-H arom. (3000) , NH (3320) ; MS , m/z (relative intensity): 462.9 [$M^{+\bullet}$] (0.7), 303.2 (6.4), 282(0.3), 180(6.7), 165.1 (48.5), 159 (1.5), 143(6.7), 134.1 (1.5), 119.1 (100), 93 (46.3), 77 (9.8) and 66(4.4).

VIIIb , IR [cm^{-1}]: C=O (arom. ketone, 1670), C=O (secondary amide, 1700), C≡N (2220), C-H aliph. (2920), C-H arom. (3040), NH (3331); MS, m/z (relative intensity): 353.2 [M-119]$^{+\bullet}$, (9.7), 313.4 (6.7) , 312 (36.7), 283.9 (11.9), 180 (7.8), 165 (100), 148.3 (19.4), 135.1 (36.7), 120.2 (12.4), 119.1 (20.3) and 93 (28.4).

Reaction of Ethyl Chloroacetate with 1-(2,4-Dimethoxyphenyl)-3-(4-chlorophenyl)prop-2-enone (Ia); Formation of Ethyl 2-(2,4-dimethoxybenzoyl)-3-(4-chlorophenyl)-1-cyclopropylcarboxylate (IX). Ethyl choloroacetate (1.0 g , 0.01 mol) was dissolved in 5 mL of absolute ethanol and the solution was cooled to 5°C in an ice bath . An ethanolic solution of 1,3-diarylprop-2-enone (**Ia**) (3.03 g , 0.01 mol in 15 mL of absolute ethanol) and a solution of sodium ethoxide (0.23 g of sodium in 10 mL of absolute ethanol) was added simultaneously with stirring and cooling (5°C) at such relative rate that **Ia** addition was completed in about 30 min and the sodium ethoxide addition was

completed in about 4 h. The reaction was refrigerated overnight , acidified with glacial acetic acid (about 2 mL) to afford a yellow solid which recrystallized from the proper solvent to give cyclopropyl derivative (**IX**).

IR [cm^{-1}]: C=C (1611), C=O (arom. ketone, 1665), C=O (ester, 1726), OH (br centered at 3400); ^{1}H-NMR (DMSO-d_6): 1.70 (t, 3H, J = 1.4 Hz, C$\underline{H}_3$-), 3.30 (s, 6H, 2 OMe), 3.90 (q, 2H, J = 1.4 Hz, C$\underline{H}_2$-CH_3), 4.90-5.20 (m, 3H, protons of cyclopropyl ring), 6.30 and 6.50 (two d, 2H, J = 3.08 Hz, C_3-H and C_5-H), 7.30-7.50 (m, 4H, arom.), 7.90 (d, 1H, J = 9.1 Hz, C_6-H); MS, m/z (relative intensity): 316.8 $[M-72]^{+\bullet}$ (0.7), 302 (25.7), 288 (2.1), 287 (11.4), 177 (30.0), 165 (100), 151.8 (18.6), 149.9 (67.8), 121.9 (20.0), 111.5 (4.6), 94 (3.6), 77 (12.9), 63 (7.9) and 42 (76.4).

Reaction of Benzyl Cyanide with 1-(2,4-Dimethoxyphenyl)-3-(3,4-methylenedioxyphenyl)prop-2-enone (Ib) ; Formation of 2-Phenyl-3-(3,4-methylenedioxyphenyl)-5-(2,4-dimethoxyphenyl)-5-oxopentanocarbonitrile (X). A solution of benzyl cyanide (2.34 g, 0.02 mol) in the least amount of dry benzene (10 mL) was stirred at rt for 10 min, then solid sodium methoxide (0.23 g of sodium metal in 10 mL of absolute methanol then evaporated till dryness) was added. Then **Ib** (3.12 g, 0.01 mol) in another 10 mL of dry benzene was added dropwise within 30 min with stirring. The reaction mixture was heated using water bath for an additional 30 min. Most of the solvent was removed and the solid that precipitated was filtered off , dried , and recrystallized from the proper solvent to give the desired product (**X**) as brown solid.

IR [cm^{-1}]: C=C (1603), C=O (1670), C≡N (2239), C-H aliph. (2937), C-H arom. (3005, 3080), OH (br centerd at 3447); ^{1}H-NMR (acetone-d_6): 3.28 (s, 6H, 2 OMe), 3.75 (d, 2H, J = 5.1 Hz, -$COCH_2$), 4.10 (m, 1H, -$COCH_2$-C$\underline{H}$), 4.65 (d, 1H, J = 7.3 Hz, -CH-CN) and 7.80-8.55 (m, 12 H, aromatic protons); MS, m/z (relative intensity): 429 $[M^{+\bullet}]$ (6.1), 335.2 (29.2), 313.6 (4.2), 312 (39.2), 297 (15.3), 165.1(100), 135.1 (65.4), 116.7 (36.5), 105.1 (12.8) and 91 (17.7).

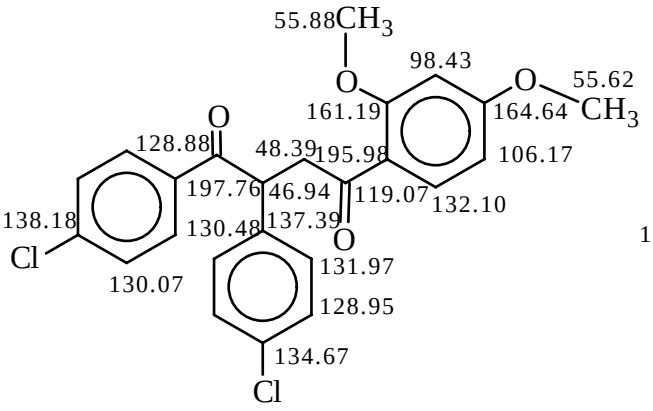
Reaction of 4-Chlorobenzaldehyde with 1,3-Diarylprop-2-enones (Ia and b); Formation of 1-(4-Chlorophenyl)-2-aryl-4-(2,4-dimethoxyphenyl)buta-1,4-diones (XIa and b). A mixture of 4-chlorobenzaldehyde (1.4 g , 0.01 mol) , sodium cyanide (0.49 g , 0.01 mol) and 1,3-diarylprop-2-enones (**Ia** and/or **b**)(0.01 mol) in dimethylformamide (20 mL) was heated under reflux with stirring for 4 h , cooled and poured into ice/water , the solid that separated out was filtered off, dried, and then recrystallized from the proper solvent to give the product (**XIa** and **b**) respectively.

XIa , IR [cm^{-1}]: two C=O (1680 and 1690), C-H aliph. (2925), C-H arom. (3075), OH (br centered at 3330) ; ^{1}H-NMR (DMSO-d_6): 2.50 (t, 1H, J = 1.4 Hz, CO-C$\underline{H}$-CH_2), 3.82 and 3.85 (two s, 6H, 2 OMe), 5.35 (dd, 2H, J = 2.5 and 2.5 Hz, CH-C$\underline{H}_2$-CO-), 6.58 and 6.61 (two d, 2H, J = 3.10 Hz, C_3-H and C_5-H), 7.32-7.69 (m, 8H, arom. of two 4-chlorophenyl groups), 8.07 (d, 1H, J = 9.10 Hz, C_6-H); MS, m/z (relative intensity): 442.1 $[M^{+\bullet}]$, (8.5), 330.6 (3.2), 329.6 (3.0), 302.6 (20.7), 251.1 (11.9), 165.1 (100),

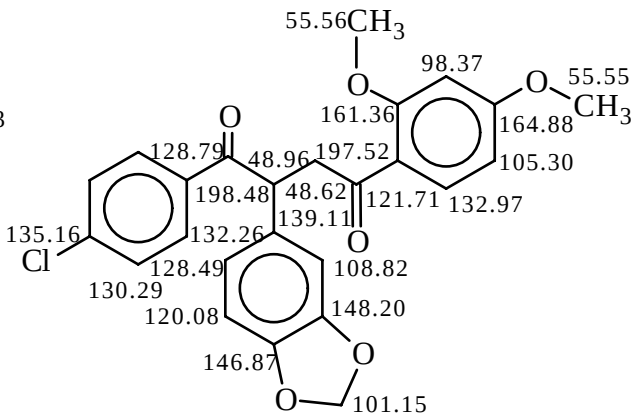
139.5 (51.9), 138.5 (51), 137 (2.2), 111.5 (7.4), 77 (5.9).

XIb , IR [cm^{-1}]: C=O of diketone (1670, 1665), C-H aliph. (2980), C-H arom. (3100), OH (br centered at 3480); ^{1}H-NMR ($CDCl_3$):2.70 (t,1H, J = 1.4 Hz, -CO-C<u>H</u>-CH_2), 3.82 and 3.84 (two s, 6H, 2 OMe), 5.10 (dd, 2H, J = 5.5 and 2.7 Hz, -CO-C<u>H</u>$_2$-CH-), 5.90 (s, 2H, O-C<u>H</u>$_2$-O), 6.43 and 6.48 (two d, 2H, J = 3.0 Hz, C_3-H and C_5-H), 6.7-7.82 (m, 7H, arom.), 7.96 (d, 1H, J = 9.1 Hz, C_6-H); MS, m/z (relative intensity): 452.2 [$M^{+\bullet}$], (20.8), 418.2 (13.0), 356.2 (3.1), 348.1 (12.3), 313.6 (26.1), 287.1 (6.3), 165.1 (100), 151 (27.2), 137 (23.1), 124 (12.3), 94 (4.6), 77 (8.5), 65 (4.4).

The ^{13}C-NMR spectra of **XIa** and **XIb** are as follows:



^{13}C-NMR of compound (XIa)



^{13}C-NMR of compound (XIb)

Hydrocyanation of Ia; Formation of 1-(4-Chlorophenyl)-4-(2,4-dimethoxyphenyl)-4-oxobutanocarbonitrile (XII). 1-(2,4-Dimethoxyphenyl)-3-(4-chlorophenyl)prop-2-enone (**Ia**) (3.03 g, 0.01 mol) was dissolved in ethanol (10 mL) and then added dropwise to potassium cyanide solution (1.0 g, 0.02 mol in 2 mL water). The reaction mixture was stirred at rt for 30 min followed by the addition of few drops of glacial acetic acid (about 1.0 mL) . The stirring was continued for an additional 30 min. The solid product which separated out was filtered off , dried, and then recrystallized from the proper solvent to afford the product (**XII**).

IR [cm^{-1}]: C=C (1607), C=O (arom Ketone, 1703), C≡N(2220), C-H aliph. (2841, 2941), C-H arom. (3050); ^{1}H-NMR ($CDCl_3$): 3.35 (s, 6H, 2 OMe), 4.10 (d, 2H, J = 7.1 Hz, -$COCH_2$), 4.80-4.85 (t, 1H, J = 4.2 Hz, -CH-CN) and 7.85-8.60 (m, 7H, aromatic protons); MS, m/z (relative intensity): 329.2 [$M^{+\bullet}$], (16.3), 302.2 (20.7), 274.1(11.11), 181 (3.6), 165 (100), 151 (5.1), 149 (6.6) 137 (3.4), 135 (4.9) and 121.2 (3.7).

Fusion of 1-(4-Chlorophenyl)-2-(3,4-methylenedioxyphenyl)-4-(2,4-dimethoxyphenyl)-buta-1,4-dione (XIb) with Hyrazine Hydrate; Formation of 3-(4-Chlorophenyl)-6-(2,4-dimethoxyphenyl)-4-(3,4-methylenedioxyphenyl)-4,5-dihydropyridazine (XIII). A mixture of **XIb** (4.5 g , 0.01 mol) and hydrazine hydrate (80%) (0.75 mL , 0.015 mol) was fused at 140-150 °C for 6 h. The reaction mixture was left to cool, triturated with 20% HCl, filtered off, the residue washed with

cold water several times, dried and finally recrystallized from the suitable solvent to afford the pyridazine derivative (**XIII**).

IR [cm^{-1}]: C=C (1590), C=N (1614), C-H aliph. (2853, 2918). The spectrum lacks two $\nu_{C=O}$ of the two aroyl groups; ^{1}H-NMR (acetone-d_6): 3.28 (s, 6H, 2 OMe), 3.85 (d, 2H, J = 7.3 Hz, CH_2), 5.10-5.20 (t, 1H, J = 4.2 Hz, CH-) 6.45 (s, 2H, -O-CH_2-O) and 7.65-8.42 (m, 10H, aromatic protons); MS, m/z (relative intensity): 448.8 [$M^{+\bullet}$] (14.3), 272.5 (11.8), 178 (100), 138.9 (10.9), 137 (18.7), 122 (23.6), 121 (21.4), 111.5 (17.4), 94 (42.6), 90 (38.2), 77 (15.8) and 65 (27.1).

Reaction of 1-(4-Chlorophenyl)-2-(3,4-methylenedioxyphenyl)-4-(2,4-dimethoxyphenyl)buta-1,4-dione (XIb) with Hydrazine Hydrate ; Formation of 2-(3,4-Methylenedioxyphenyl)-3-(2,4-dimethoxybenzoyl)propan-1-one hydrazone (XIVa). A mixture of **XIb** (4.5 g , 0.01 mol) and 80% hydrazine hydrate (0.75 mL , 0.015 mol) in ethanol (30 mL) was refluxed for 6 h , most of the solvent was distilled off then the reaction mixture was poured into ice/10% HCl. The crude product which separated out was filtered off , washed several times with water, dried then recrystallized from the proper solvent to afford the mono hydrazone derivative (**XIVa**).

IR [cm^{-1}]: C=N (1599), C=O (1657), NH (br centered 3350); ^{1}H-NMR (acetone-d_6): 3.35 (s, 6H, 2OMe), 3.80 (br s, 2H, NH_2), 3.95 (d, 2H, J = 6.8 Hz, -$COCH_2$), 5.10-5.15 (t, 1H, J = 4.1 Hz. -$COCH_2$-C<u>H</u>-) and 7.85-8.62 (m, 11H, aromatic protons); MS , m/z (relative intensity) : 466.5 [$M^{+\bullet}$] (13.0), 467.6 [M+1]$^{+\bullet}$ (4.1), 451.5 (8.3), 416 (23.9), 339 (14.6), 312 (42.9), 165 (100), 154.5 (10.1), 151 (27.4), 146 (18.4), 138.5 (29.2), 137 (33.4), 124 (22.3), 120 (28.7), 111.5 (11.9), 94 (18.3), 77 (28.8) and 65 (34.4).

Reaction of 1-(4-Chlorophenyl)-2-(3,4-methylenedioxyphenyl)-4-(2,4-dimethoxyphenyl)buta-1,4-dione (XIb) with Hydroxylamine Hydrochloride; Formation of 2-(3,4-methylenedioxyphenyl)-3-(2,4-dimethoxybenzoyl)propan-1-one oxime (XIVb). A mixture of **XIb** (4.5 g , 0.01 mol) and hydroxylamine hydrochloride (1.4 g , 0.015 mol) in pyridine (20 mL) was refluxed for 6 h , most of the solvent was distilled off then the reaction mixture was poured into ice/ 10% HCl. The crude product was separated out, filtered off, washed several times with water, dried then recrysttlized from the proper solvent to afford the monoxime derivative (**XIVb**).

IR [cm^{-1}]: C=N (1611), C=O (1680), OH (br centered at 3447); ^{1}H-NMR ($CDCl_3$): 3.30 (s, 6H, 2 OMe), 3.92 (d, 2H, J = 6.1 Hz, -$COCH_2$), 5.15-5.20 (t, 1H, J = 4.1 Hz -$COCH_2$-C<u>H</u>-), 7.90-8.55 (m, 11H, aromatic protons) and 11.30 (s, 1H, OH); MS , m/z (relative intensity) : 467.5 [$M^{+\bullet}$] (8.4), 468.5 [M+1]$^{+\bullet}$ (3.2), 453.5 (11.8), 418 (18.7), 441 (10.7), 312 (37.3), 165 (100), 155.5 (13.6), 151 (21.8), 146 (17.8), 138.5 (19.2), 137 (31.8), 124 (22.3), 120 (23.8), 111.5 (13.2), 94 (18.8), 77 (18.3) and 65 (31.7).

Table 1 : Physical Characteristics of New Compounds*

Compd	mp[˚C] yield (%)	Solvent of ** recrystallization (Color)	Mol. Formula	Analysis (%) Found/Calcd C	H	N	S
Ia	110-111	L.P	$C_{17}H_{15}O_3Cl$	68.09	5.05		
	96	(Pale Yellow)		67.74	4.96		
Ib	136-138	L.P	$C_{18}H_{16}O_5$	69.51	5.01		
	92	(Pale Yellow)		69.23	5.13		
IIa	125-126	E	$C_{20}H_{16}N_3O_2Cl$	67.37	4.56	11.42	
	95	(Pale Brown)		67.20	4.53	11.20	
IIb	117-119	E	$C_{21}H_{17}N_3O_4$	66.00	4.50	11.66	
	92	(Pale Brown)		65.66	4.38	11.49	
IIIa	155-157	M	$C_{20}H_{18}N_3O_3Cl$	64.28	4.88	10.82	
	93	(Yellow)		64.12	4.83	10.69	
IIIb	176-177	M	$C_{21}H_{19}N_3O_5$	62.85	4.78	11.02	
	90	(Yellow)		62.58	4.69	10.95	
IVa	140-142	M	$C_{21}H_{16}N_3O_2ClS_2$	57.10	3.76	9.65	14.57
	85	(Brown)		57.08	3.62	9.51	14.50
IVb	132-134	M		58.78	3.83	9.55	14.30
	83	(Brown)	$C_{22}H_{17}N_3O_4S_2$	58.54	3.77	9.31	14.19
V	205-207	M		56.84	3.50	9.39	14.37
	86	(Brown)	$C_{21}H_{16}N_3O_2ClS_2$	57.08	3.62	9.51	14.50
VIa	143-145	B		64.45	4.33	11.31	6.46
	93	(Bright Yellow)	$C_{27}H_{21}N_4O_2ClS$	64.74	4.20	11.19	6.39
VIb	146-147	L.P		65.67	4.22	10.84	6.17
	90	(Bright Yellow)	$C_{28}H_{22}N_4O_4S$	65.88	4.31	10.98	6.27
VIIa	160-161	M		61.48	4.39	16.97	
	80	(Brown)	$C_{21}H_{18}N_5O_2Cl$	61.84	4.42	17.18	
VIIb	188-190	E		63.19	4.42	16.66	
	75	(Brown)	$C_{22}H_{19}N_5O_4$	63.31	4.56	16.79	
VIIIa	256-258	B		67.31	4.81	5.90	
	90	(Pale Brown)	$C_{26}H_{23}N_2O_4Cl$	67.46	4.97	6.05	
VIIIb	107-109	B		68.46	4.96	5.87	
	85	(Pale Brown)	$C_{27}H_{24}N_2O_6$	68.64	5.08	5.93	

Table 1 (Cont.)

Compd	mp[˚C] yield (%)	Solvent of recrystallization (Color)	Mol. Formula	Analysis (%) Found/Calcd C	H	N	S
IX	190-191	E	$C_{21}H_{21}O_5Cl$	64.59	5.36		
	60	(Yellow)		64.86	5.41		
X	> 300	B/L.P	$C_{26}H_{23}NO_5$	72.66	5.23	3.18	
	65	(Brown)		72.73	5.36	3.26	
XIa	140-142	M	$C_{24}H_{20}O_4Cl_2$	64.86	4.46		
	60	(Brown)		65.01	4.51		
XIb	131-132	M	$C_{25}H_{21}O_6Cl$	65.98	4.57		
	62	(Brown)		66.30	4.64		
XII	142-143	B/L.P	$C_{18}H_{16}NO_3Cl$	65.73	4.74	4.19	
	57	(Pale Red)		65.55	4.86	4.25	
XIII	145-147	E	$C_{25}H_{21}N_2O_4Cl$	66.44	4.56	6.00	
	54	(Pale Brown)		66.89	4.68	6.24	
XIVa	140-142	E	$C_{25}H_{23}N_2O_5Cl$	64.53	4.50	6.16	
	67	(Brown)		64.31	4.39	6.00	
XIVb	155-156	B/L.P	$C_{25}H_{22}NO_6Cl$	63.87	4.66	2.76	
	62	(Brown)		64.17	4.71	2.99	

** E = Ethanol , M = Methanol , B = Benzene , L.P = Light petroleum (80-100˚C).

Table 2 : MIC of some of the synthesized compounds against E. coli and S. aureus using standard broth dilution method ranging from 1-128 µg/mL.

Compd	Minimum Inhibitory Concentration (MIC) µg/mL	
	E. coli (G -ve)	S. aureus (G +ve)
Ia	64 µg/mL	128 µg/mL
Ib	128	128
IIb	128	32
IIIb	8	4
IVa	64	64
IVb	16	64
VIIb	2	4
XIb	32	16

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