Utility of anilides as building block to synthesize some heterocyclic compounds for biological evaluation : New synthesis of dihydropyridine , pyrazolo[1,5-*a*] pyrimidine and thiazolo[3,2-*a*] pyrimidine derivatives

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Dedicated to the Memory of Prof.A.A.Elagamey

ABSTRACT- Several new dihydropyridine , pyrazolo[1,5-*a*] pyrimidine and thiazolo[3,2-*a*] pyrimidine derivatives have been prepared by using β-ketoanilides **1** and arylmethylenemalononitriles **2** as starting materials and as key intermediates for biological evaluation.

Keywords:Arylmethylenemalononitriles,dihydropyridines,pyrazolo[1,5-*a*] pyrimidines,thiazolo[3,2-*a*]pyrimidines
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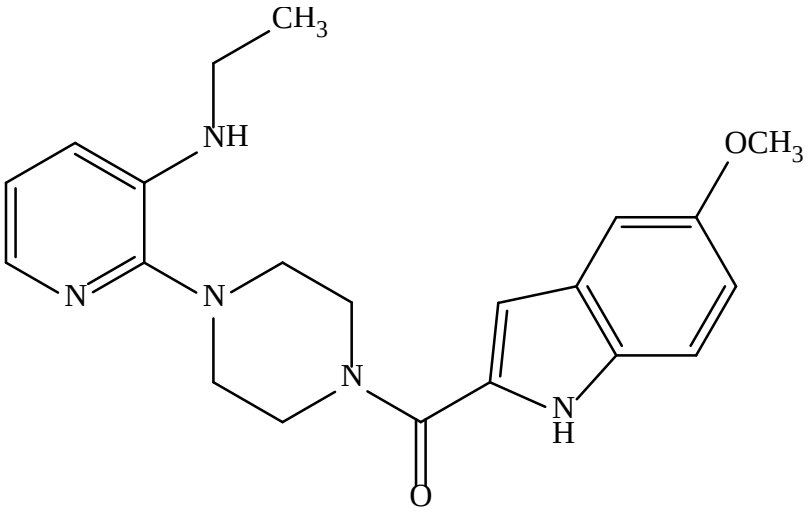
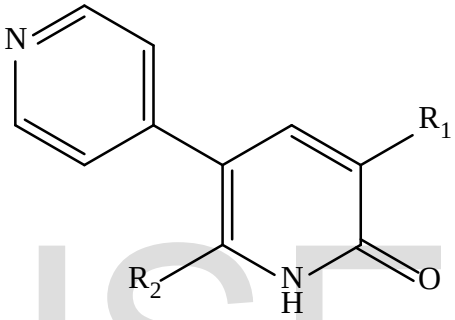
Abstracted from her M.Sc.Thesis.

1. Introduction :

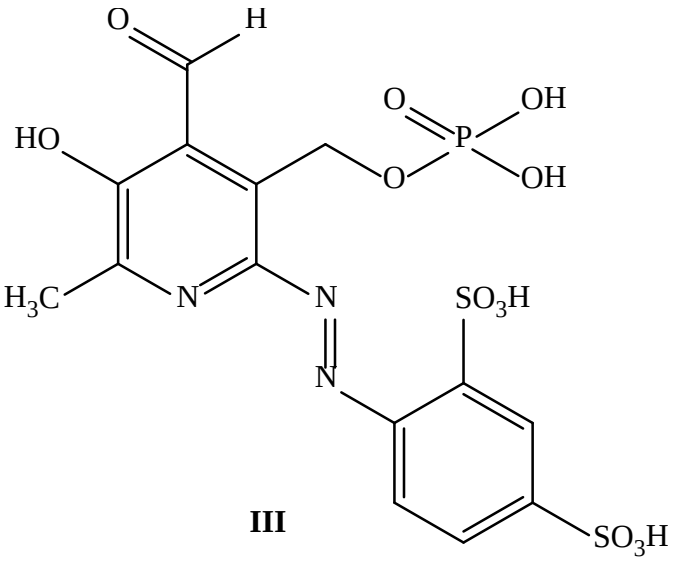
Certain polyfunctionally substituted pyridines are potent inhibitors of the human immunodeficiency virus type **1** (HIV-1) reverse transcriptase . For example ,ateviridine **I** has been selected for further clinical evaluation as anti- HIV agent [1],the dihydropyridines,*e.g*.adalate ,are still the most widely used calcium channel blockers [2]. Certain functionally substituted pyridones, *e.g* .amrinone **IIa** [3] and milrinone **IIb** [4],are used for treatment of congestive heart failure.Compounds **III** have been proved to be selective antagonists of P2 receptrors for neurotransmitters[3] .



I



IIa,R_1 = H ; R_2 = NH_2
b,R_1 = CH_3 ; R_2= CN



III

In the past few years ,we have been involved in a program aiming to develop new simple routes for the synthesis of different heterocyclic compounds of biological interest to be evaluated as biodegradable agrochemicals[5-11] .

In conjunction to previous interest in developing syntheses of polyfunctionally substituted heteroaromatics utilizing readily obtainable and inexpensive starting components[5-11],we report here on syntheses of dihydropyridine ,pyrazolo[1,5-*a*] pyrimidine and thiazolo[3,2-*a*] pyrimidine derivatives using β-ketoanilides **1** and arylmethylenemalononitriles **2** as starting materials and as key intermediates for biological evaluation.

2. EXPERIMENTAL :

All melting points are uncorrected and measured on Griffin&George MBF 010T (London) apparatus. Recorded yield correspond to the pure products. IR (KBr) spectra were recorded on a Perkin Elmer SP-880 spectrometer and ^{1}H-NMR spectra: were measured on Varian 270 MHz spectrometer on DMSO-d_6 as solvent and TMS an internal standard. Chemical shifts are reported in δ units (ppm). Microanalyses were performed on a LECO CHN-932 elemental analyzer and carried out in the Microanalytical Data Unit at Cairo and Damietta Universities. Mass spectra were recorded on a MS 30(AEI) instrument at 70 eV ionization energy .

Formation of β-ketoanilides **2a-e :**
A solution of (0.01mole) of β-ketoesters **2a,b** and (0.01mole) of primary aromatic amines in dry xylene (100ml) were refluxed for six hours at 150^{o}C.The solvent was then concentrated to its half volumeand then left to cool to room temperature.The solids precipitated were colleted by filtration ,recrystallised and then identified as **2a-e** [12,13].

Preparation of 6-amino-1,4-diaryl-5-benzoyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitriles **6a-e** :
A solution of β-ketoanilides **2a-e** (0.01mole) in ethanol (50ml) was treated (0.01mole) of arylmethylenemalononitriles **3** and few drops of piperidine were refluxed for three hours .The solids deposited were collected by filtration ,recrystallised from the proper solvents and then identified as **6a-e**.

2-Amino-5-benzoyl-1-(4-nitrophenyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile **6a** : Formed colorless crystals in 75 % yield , from ethanol ,m.p.273-275^{o}C ; IR (ν /cm^{-1}): 3433, 3342 (NH_2) , 2187(conjugated CN),1703(CO),1641(CO);^{1}H-NMR (DMSO-d_6)(δ,ppm) : 4.35-4.36 (d,J = 3Hz,1H,CH) 5.12-5.15(d,J=3Hz,1H,CH), 5.78 (s,2H, NH_2),7.27-8.39 (m,14H, aromatic protons); ^{13}C-NMR (DMSO-d_6)(δ, ppm) :41.60(C-4),58.28(C-3),61.60(C-5),119.93(CN),128.35-154.54 (aromatic carbons),196.04(CO),206.16(CO).*Anal*. Calcd.for $C_{25}H_{18}N_4O_4$ (438.43): C,68.49; H, 4.14; N , 12.78. Found: C,68.65 ; H,4.25; N,12.53.

2-Amino-5-benzoyl-4-(4-methoxyphenyl)-6-oxo-1-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile **6b** : Formed colorless crystals in 70 % yield , from ethanol ,m.p.246-248^{o}C ; IR (ν /cm^{-1}): 3450, 3321 (NH_2) , 2190(conjugated CN),1697(CO),1643(CO);^{1}H-NMR (DMSO-d_6)(δ,ppm) : 3.77(s,3H,OCH_3),4.23-4.26 (d,J = 3Hz,1H,CH.) 5.02-5.03(d,J=3Hz ,1H, CH), 5.42 (s,2H, NH_2),6.94-8.09 (m,14H, aromatic protons); ^{13}C-NMR (DMSO-d_6) (δ,ppm) :40.61(C-4),55.52(C-3),60.63(C-5),115.15 (CN), 120.37-167.70 (aromatic carbons),196.04 (CO),206.16(CO).*Anal*. Calcd.for $C_{26}H_{21}N_3O_3$ (423.46): C,73.74; H,5.00; N , 9.92. Found: C,73.67 ; H,5.11; N,9.86.

2-Amino-5-benzoyl-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-6-oxo-*1,4,5,6- tetrahydropyridine-3-carbonitrile* **6c** : Formed faint yellow crystals in 65 % yield , from ethanol / 1,4-dioxan ,m.p.241-243^{o}C ; IR (ν /cm^{-1}): 3444, 3355 (NH_2) , 2183(conjugated CN),1710(CO), 1671(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm) : 3.76(s,3H,OCH_3),4.30-4.31 (d,J = 3Hz ,1H, CH.) 5.11-5.73(d,J=3Hz ,1H, CH), 6.91 (s,2H, NH_2),7.40-8.38 (m , 13H, aromatic protons); ^{13}C-NMR (DMSO-d_6) (δ,ppm) :41.71(C-4), 57.74 (C-3), 61.45 (C-5),125.18 (CN), 120.04-167.93 (aromatic carbons) , 196.13 (CO) 206.42 (CO).*Anal*. Calcd.for $C_{26}H_{20}N_4O_5$ (468.46):C,66. 66; H,4.30; N , 11.96. Found: C,66.44 ; H,4.11; N,11.84.

6-Amino-3-benzoyl-2-oxo-4-phenyl-3,4-dihydro-2*H*-[1,2'-bipyridine]-5-carbonitrile **6d** : Formed yellow crystals in 68 % yield , from ethanol / 1,4-dioxan ,m.p.187-189^{o}C ; IR (ν /cm^{-1}): 3444, 3355 (NH_2) , 2184 (conjugated CN),1700(CO), 1675(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm) : 4.34-4.35 (d,J = 3Hz ,1H, CH) 5.10-5.12(d,J=3Hz ,1H, CH), 5.69 (s,2H, NH_2),7.27-8.63 (m , 14H, aromatic protons); ^{13}C-NMR (DMSO-d_6)

(δ,ppm) :41.71(C-4), 57.75 (C-3), 61.45 (C-5),120.07 (CN), 125.31-167.81 (aromatic carbons) ,195.74 (CO) 206.42 (CO).*Anal*. Calcd.for $C_{24}H_{18}N_4O_2$ (394.43): C,73.08; H,4.60; N , 14.20. Found: C,73.23 ; H,4.34; N,14.35.

6-Amino-3-benzoyl-2-oxo-4-(4-methoxyphenyl-3,4-dihydro-2*H*-[1,2'-bipyridine]-5-carbonitrile **6e** : Formed yellow crystals in 65 % yield , from ethanol / dimethylformamide ,m.p.187-189^oC ; IR (ν /cm^{-1}): 3444, 3417 (NH_2) , 2191 (conjugated CN),1701(CO), 1674(CO); ^{1}H-NMR (DMSO-d_6)(δ,ppm) :3.77(s,3H,)CH_3), 4.29-4.30 (d,J = 3Hz ,1H, CH) 5.06-5.07(d,J=3Hz ,1H, CH), 5.64 (s,2H, NH_2),6.90-8.62 (m , 13H, aromatic protons); ^{13}C-NMR (DMSO-d_6) (δ,ppm) :40.98(C-4), 55.52 (C-3), 62.02 (C-5),120.09 (CN), 125.26-167.91 (aromatic carbons) ,195.80 (CO) 206.23 (CO).*Anal*. Calcd.for $C_{25}H_{20}N_4O_3$ (424.45): C,70.74; H,4.75; N , 13.20. Found: C,74.42 ; H,4.34; N,13.35.

2-Amino-3-arylazo-5-pyrazolo[1,5-a]pyrimidin-7(6H)-ones **10a-c**
Method A:
A mixture of β-ketoanilides **2a-d** (0.01 mole) and (0.01 mole) of 4-arylazo-3,5-diaminopyrazloe **7a-c** in glacial acetic acid (30ml) were heated under reflux for three hours.The solvent was then evaporated in *vacuo* and the resulting solid products were collected by filtration ,recrystallised from the suitable solvents and then identified as **10a-c** .
Method B:

Compounds **10a-c** were also prepared by reacting (0.01 mole) of β-ketoesters **1a,b** and (0.01 mole) of 4-arylazo-3,5-diaminopyrazloe **7a-c** under theabove reaction conditions.

2-Amino-3-(3-chlorophenyl)diazenyl)-5-phenylpyrazolo[1,5-a] pyrimidine-7(6H)-one **10a** : Formed red crystals in 65 % yield, from ethanol ,m.p.>300^oC ; IR (ν /cm^{-1}): 3479, 3124 (NH_2,OH) , 1689(CO) ,1643 (N=N); ^{1}H-NMR (DMSO-d_6)(δ,ppm) :2.73(s,2H, CH_2), 6.52(s,1H, CH-), 7.01(s,2H, NH_2), 7.32-7.99 (m , 9H, aromatic protons) ,11.92 (brs., 1H , OH) .*Anal*. Calcd.for $C_{18}H_{13}ClN_6O$ (364.79): C,59.27; H,3.59; N , 23.04. Found: C,74.42 ; H,3.34; N,23.35.

2-Amino-3-(4-chlorophenyl)diazenyl)-5-phenylpyrazolo[1,5-a] pyrimidine-7(6H)-one **10b** : Formed reddish brown crystals in 75 % yield, from ethanol / dimethylformamide ,m.p.294-296^oC ; IR (ν /cm^{-1}):

3487, 3253 (NH_2,OH) , 1679(CO) ,1633 (N=N); ^{1}H-NMR (DMSO-d_6) (δ,ppm) :2.49 (s,2H, CH_2), 6.50(s,1H, CH), 7.15(s,2H, NH_2), 7.18-7.97 (m , 9H, aromatic protons) ,10.98 (brs., 1H , OH) .*Anal.* Calcd.for $C_{18}H_{13}ClN_6O$ (364.79): C,59.27; H,3.59; N , 23.04. Found: C,74.53 ; H,3.34; N,23.22.

2-Amino-3-(4-methoxyphenyl)diazenyl)-5-methylpyrazolo[1,5-a] pyrimidine-7(6H)-one **10c** : Formed reddish brown crystals in 70 % yield, from ethanol / dimethylformamide ,m.p.279-281^{o}C ; IR (ν /cm^{-1}): 3487, 3276(NH_2,OH) , 1681(CO) ,1630 (N=N); ^{1}H-NMR (DMSO-d_6) (δ,ppm) :2.31(s,3H,CH_3),2.45 (s,2H, CH_2), 5.55(s,1H, CH), 6.45(s,2H, NH_2), 6.90-7.00 (d,J=7Hz, 2H, aromatic protons) , 7.80-7.85 (d,J=7Hz, 2H, aromatic protons),10.21 (brs., 1H , OH) .*Anal.* Calcd.for $C_{14}H_{14}N_6O_2$ (298.30): C,56.37; H,4.73; N , 28.17. Found: C,56.35 ; H,4.66; N,28.31.

4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides **13a-c**

A mixture of β-ketoanilides **2a,d** (0.01mole), aromatic aldehydes (0.01mole) and (0.01mole) of thiourea in ethanol (50ml) containing few drops of HCl were refluxed for six hours .The reaction mixture was left to cool at room temperature and the precipitates formed were collected by filtration ,recrystallised from the suitable solvents and then identified as **13a-c** .

N,4,6-triphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide **13a** : Formed colorless crystals in 70 % yield, from ethanol ,m.p.250-252^{o}C ; IR (ν /cm^{-1}): 3413, 3168(NH),1668 (CO) ,1203 (C=S); ^{1}H-NMR (DMSO-d_6) (δ,ppm) : 5.32(s,1H, H-4), 6.91-7.73 (m,15H, aromatic protons) , 9.12 (s, 1H , NH), 9.58 (s, 1H , NH), 10.17 (s, 1H , NH) .*Anal.* Calcd.for $C_{23}H_{19}N_3OS$ (385.48): C,71.66; H,4.97; N , 10.90. Found: C,71.73 ; H,4.68; N,10.82.

4-(4-Methoxyphenyl)-N, 6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine -5-carboxamide **13b** : Formed colorless crystals in 68 % yield, from ethanol /dimethylformamide ,m.p.275-277^{o}C ; IR (ν / cm^{-1}): 3263, 3165(NH),1652 (CO) ,1203 (C=S); ^{1}H-NMR (DMSO-d_6) (δ,ppm) :3.66(s,3H,OCH_3), 5.27(s,1H, H-4), 6.93-7.44 (m,14H, aromatic protons) , 9.10 (s, 1H , NH), 9.47 (s, 1H , NH), 10.07 (s, 1H , NH) .*Anal.*

Calcd.for $C_{24}H_{21}N_3O2S$ (415.51): C,69.37; H,5.09; N , 10.11. Found: C,69.23 ; H,5.22; N,11.33.

6-Methyl-4-phenyl-2-thioxo-N-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide **13c** : Formed colorless crystals in 70 % yield, from ethanol ,m.p.228-230^{o}C ; IR (ν /cm^{-1}): 3456, 3282(NH),1700 (CO) ,1203 (C=S); ^{1}H-NMR (DMSO-d_6) (δ,ppm) :2.26(s,3H,CH_3),2.34(s,3H,CH_3), 5.40 (s,1H, H-4), 7.17-7.33 (m,9H, aromatic protons) , 9.12 (s, 1H , NH), 10.12 (s, 1H , NH), 13.76 (s, 1H , NH) .*Anal*. Calcd.for $C_{19}H_{19}N_3OS$ (337.44): C,67.63; H,5.68; N , 12.45. Found: C,67.54 ; H,5.71; N,12.34.

Preparation of thiazolo[*3,2-a*]*pyrimidines* **15a,b**

Method A:

A mixture of pyrimidinethiones **13a,c** (0.0mole) and ethyl bromoacetate (0.0mole) in alcoholic potassium hydroxide was heated under reflux for five hours .The reaction mixture was then left to cool to room temperature .The solid products formed after pouring on ice was neutralized with dilute hydrochloric acid were collected by filtration ,recrystallised from the proper solvents and then identified as **15a,b**.

Method B:

A mixture of pyrimidinethiones **13a,c** (0.0mole) and ethyl chloroacetyl chloride (0.0mole) in ethanol was refluxed for one hour on steam bath and the precipitates formed were collected by filtration ,recrystallised from the suitable solvents abd then identified as **15a,b**.

3-Oxo-N,5,7-triphenyl-3,5-dihydro-2H-thiazolo[3,2-a]pyrimdine-6-carboxamide **15a** : Formed colorless crystals in 65 % yield, from ethanol ,m.p.225-227^{o}C ; IR (ν /cm^{-1}): 3414, 3325(NH),1716 (CO) ,1654 (C=O); ^{1}H-NMR (DMSO-d_6) (δ,ppm) : 3.76(s,2H,CH_2),6.15 (s,1H, H-4), 6.92-7.54 (m,15H, aromatic protons) , 10.15 (s, 1H , NH).*Anal*. Calcd.for $C_{25}H_{19}N_3O_2S$ (425.50): C,70.57; H,5.50; N , 9.88. Found: C,70.43 ; H,5.66; N,9.63.

7-Methyl-3-oxo-5-phenyl-N-(p-tolyl)-3,5-dhydro-2H-thiazolo[3,2-a] pyrimdine-6-carboxamde **15b** : Formed orange crystals in 60 % yield, from ethanol ,m.p.287-2289^{o}C ; IR (ν /cm^{-1}): 3438, 3325(NH),1707 (CO) ,1647 (C=O); ^{1}H-NMR (DMSO-d_6) (δ,ppm) :

2.34(s,3H,CH_3),2.92(s,3H,CH_3),3.74(s,2H,CH_2),6.17 (s,1H, H-4), 7.17-7.33 (m,9H, aromatic protons) , 10.13 (s, 1H , NH).*Anal*. Calcd.for $C_{21}H_{19}N_3O_2S$ (377.46): C,6.82; H,5.07; N , 11.13. Found: C,66.70 ; H,5.16; N,11.23.

3.RESULTS AND DISCUSSIN :

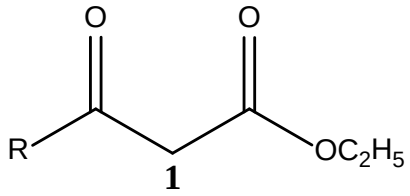
It has been found that, β-ketoanilides **2a-e**[12,13] prepared by condensation of β-ketoesters **2a,b** with primary aromatic amines . Compounds **2a,b** reacted with arylmethylenemalononitriles **3a,b** in refluxing ethanol and in presence of catalytic amounts of piperidine to give the addition products,for which 6-amino-4-aryl-5-cyano-4*H*-pyran-3-(*N*-aryl) carboxamide **5** or 6-amino-1,4-diaryl-5-benzoyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitriles **6** . 6-Amino-4-aryl-5-cyano-4*H*-pyran-3-(*N*-aryl)carboxamides **5** were readily eliminated on the basis of ^{1}H-NMR spectra which clearly indicate the absence of any signals corresponding to 4*H*-pyran protons at δ = 4.5 - 5.0 ppm.Thus,6-amino-1,4-diaryl-5-benzoyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitriles **6** were established as a reaction products. Compounds **6** were proposed to be formed *via* Michael type addition of the active methylene group in the β-ketoanilides **2** to the π-deficient double bond in the arylmethylenemalononitriles **3** to give the Michael adduct **4** ,then cyclised to give 6-amino-1,4-diaryl-5-benzoyl-2-oxo-1,2,3,4-tetrahydropyridine-3-carbonitriles **6** .

β-ketoanilides **2a-d** reacted with 4-arylazo-3,5-diaminopyrazoles **7a-c** in refluxing glacial acetic acid to give products for which pyrazolo[1,5-*a*] pyrimidines **9** and **10** were expected .However,structures were readily eliminated on the basis of their analytical and spectral data. Thus, pyrazolo[1,5-*a*]pyrimidines **10** were established for the products. Compounds **10** were assumed to be formed *via* first condensation of the carbonyl group in the β-ketoanilides **2a-d** with the exocyclic amino function in 4-arylazo-3,5-diaminopyrazoles **7a-c** *via* water elimination to give the intermediates **8**.These were cyclised through primary aromatic amines elimination to yield the final isolable products **10**a-c.

It has been reported that ,aryldihydropyrimidines have recently received great attention because of their wide range of therapeutic and pharmacological properties [14,15].Also,the chemistry of 1,2,3,4-

tetrahydropyrimidine-2-thiones have attracting wide range of attention. The present popularity of these tetrahydropyrimidines is mainly because of their structural relationship to the clinically important dihydropyridine calcium-channel blockers and related compounds. 1,2,3,4-tetrahydropyrimidine-2-thiones are known as versatile heterocyclic reragents that have been subjected to a large variety of structural modification in order to prepare derivatives withdifferent biological activities.Several synthetic routes have been described for synthesis of condensed pyrimidine derivatives[16-18].Based on these literature reports ,in this study ,synthesis and structural establishment of 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides**13a-c**.Compounds **13a-c** were synthesized by refluxing an equimolecular amounts of β-ketoanilides **2a,d** aromatic aldehydes and thiourea **12** in ethanol containing few drops of HCl .Analytical and spectral data are in full agreement with structures **13a-c** (*c.f.*experimental) . Compounds **13a-c** were proposed to be obtained through first condensation of β-ketoanilides **2a,d** with the aromatic aldehydes to form the arylidene derivatives **11** and the cyclocondensed with the appropriate amount of thiourea**12** to yield 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides**13a-c**.

4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides **13a,c** were condensed with ethyl bromoacetate in ethanol and in the presence of potassium hydroxide as catalyst to give the corresponding 2H-thiazolo[3,2-a]pyrimdine-6-carboxamide**s 15a,b** . Elucidation of structures **15a,b** was based on their correct values of elemental analysis and spectral data.We have also found that the same compounds **15a,b** were obtained when 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamides**13a,c** were subjected to react with chloroacetyl chloride in refluxing ethanol containing catalysed by triethyl amine .



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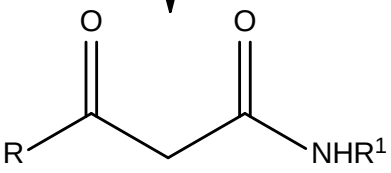
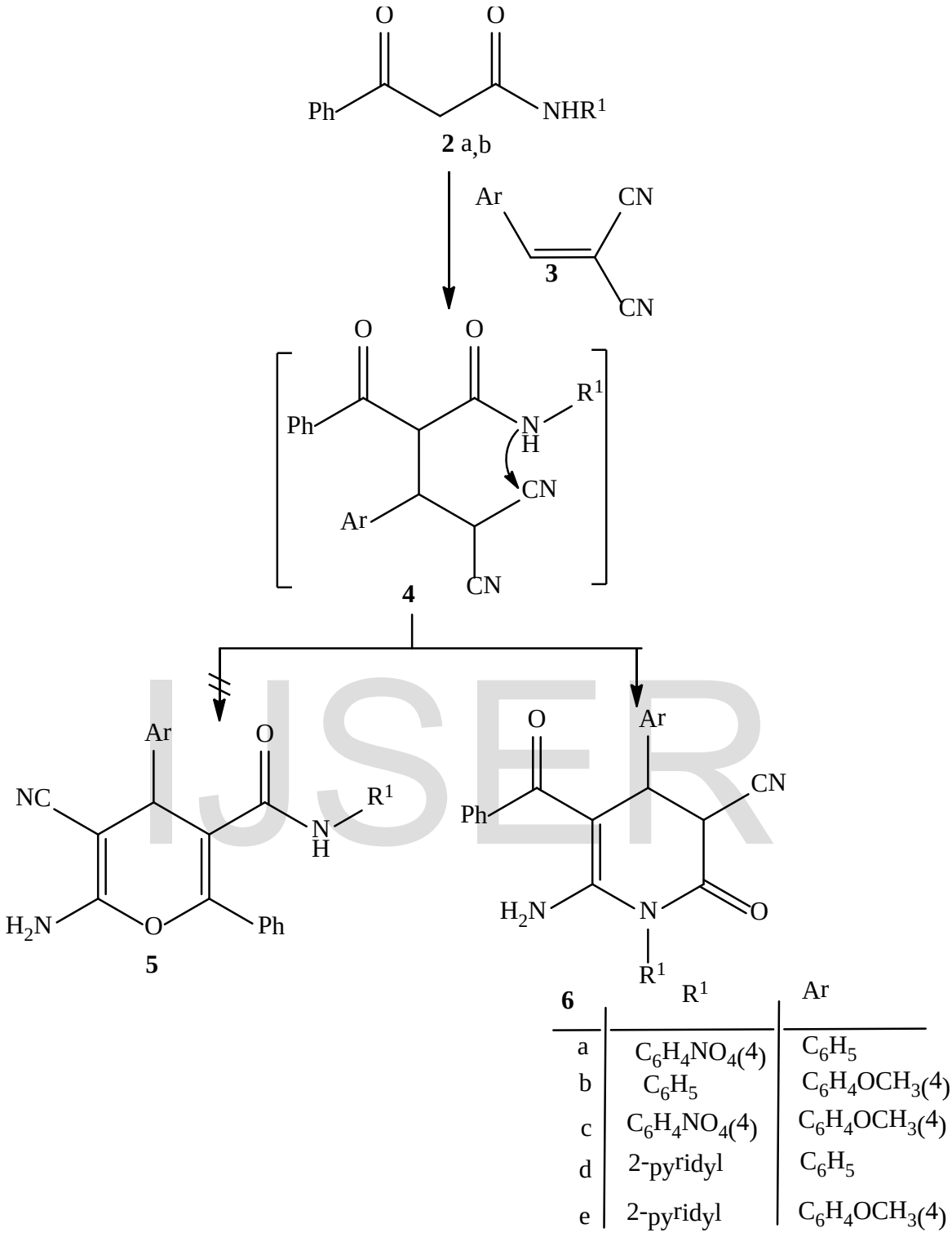
R^1NH_2 / Xylene / 150°C



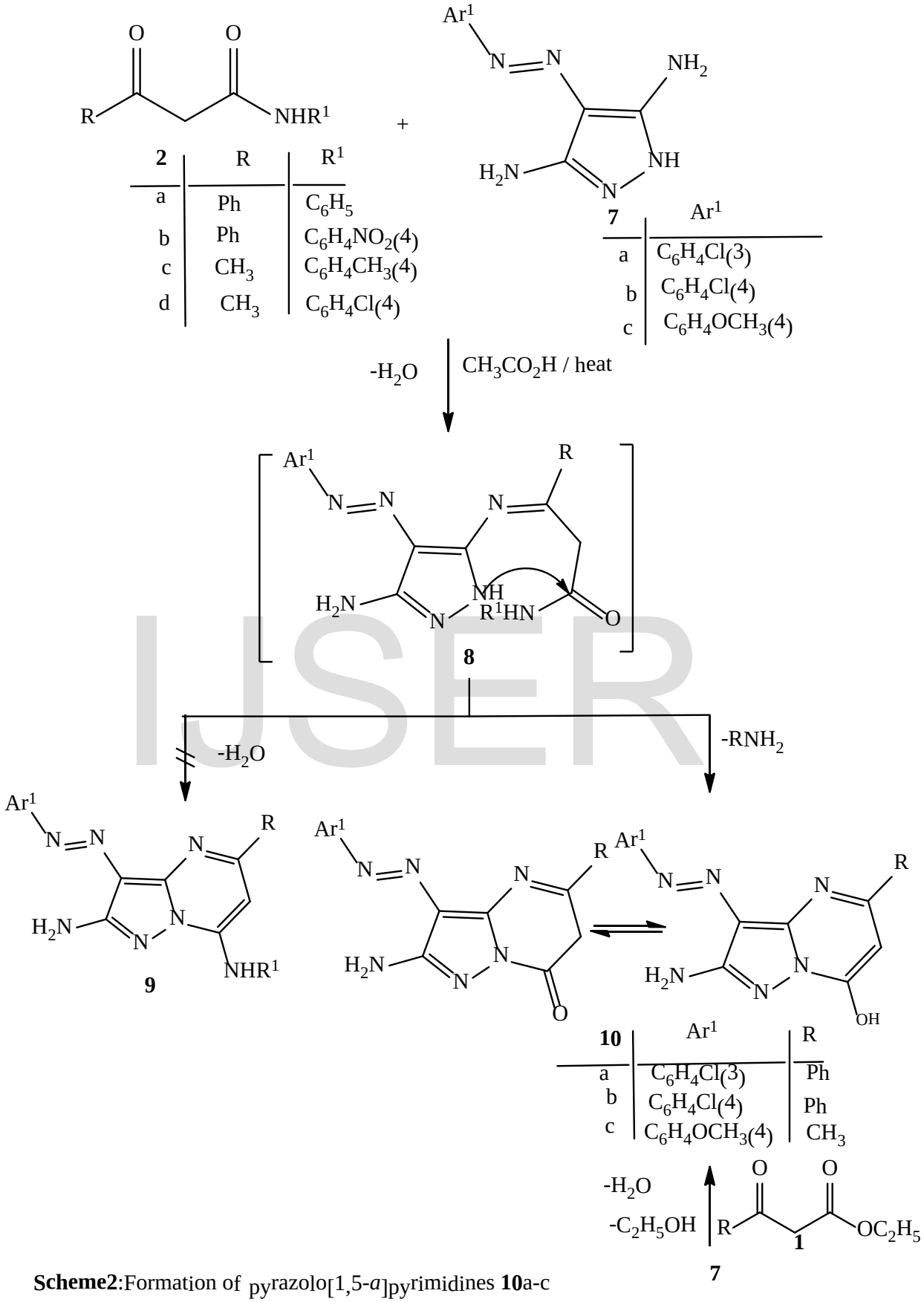
2

	R	R^1
a	Ph	C_6H_5
b	Ph	$C_6H_4NO_2(4)$
c	Ph	2-pyridyl
d	CH_3	$C_6H_4CH_3(4)$
e	CH_3	$C_6H_4Cl(4)$

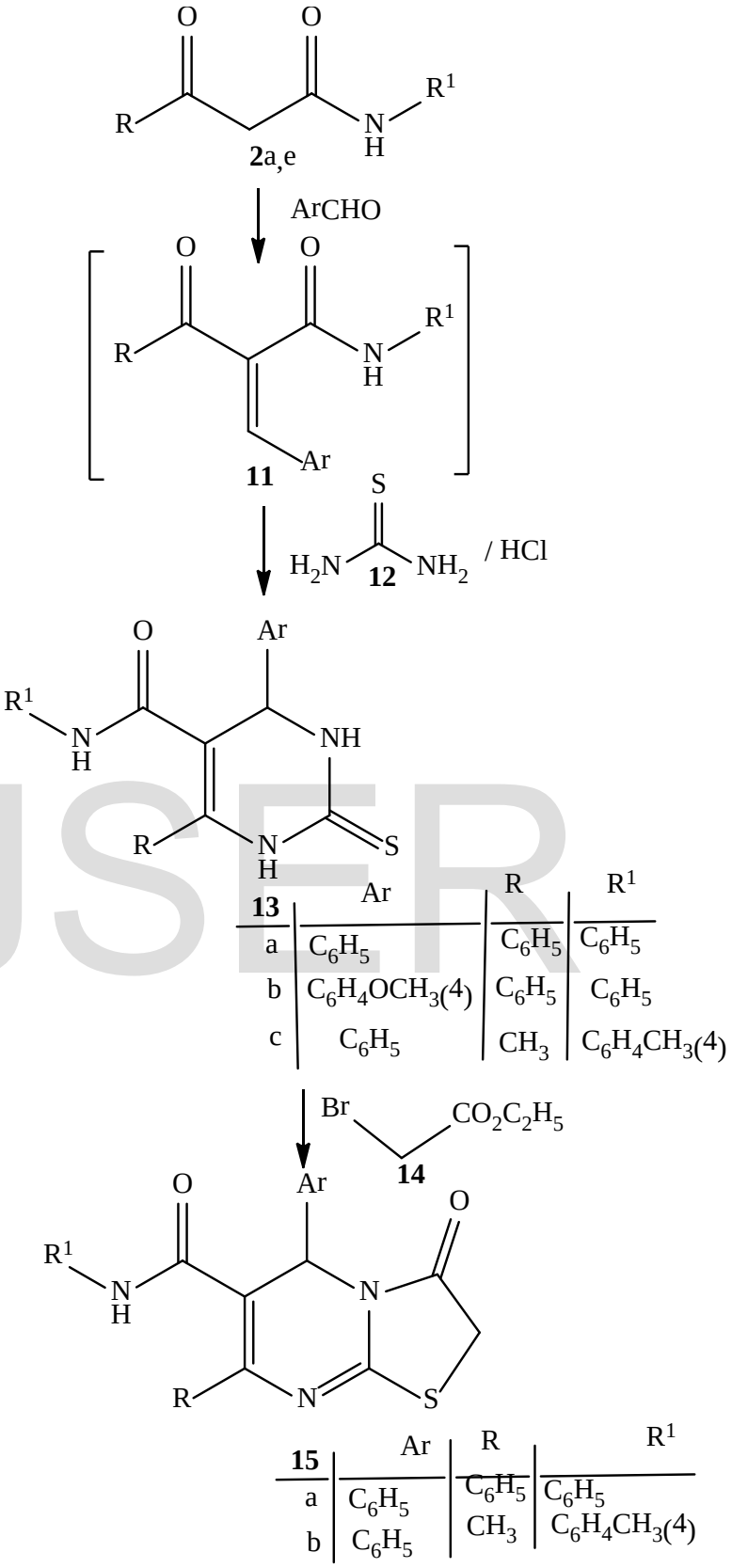


6	R^1	Ar
a	$C_6H_4NO_4(4)$	C_6H_5
b	C_6H_5	$C_6H_4OCH_3(4)$
c	$C_6H_4NO_4(4)$	$C_6H_4OCH_3(4)$
d	2-pyridyl	C_6H_5
e	2-pyridyl	$C_6H_4OCH_3(4)$

Scheme 1: Synthesis of the pyridines **6** a-e



Scheme2:Formation of pyrazolo[1,5-*a*]pyrimidines **10**a-c



Scheme 3 :Preparation of thiazolopyrimidines **14** a,b

Conclusion

We conclude that,several new dihydropyridine , pyrazolo[1,5-*a*] pyrimidine and thiazolo[3,2-*a*] pyrimidine derivatives were synthesized using β-ketoanilides **1** and arylmethylenemalononitriles **2** as readily obtainable and inexpensive starting materials and as key intermediates for biological evaluation.

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