Some Fused/Isolated Heterocyclic of Pyrimidine, β-Lactam, Thiazolidine and Triazine Derivatives

H.A. Soleiman*

Chemistry Department, Aswan Faculty of Science, South Valley University, Aswan, Egypt

Abstract: Fused/isolated heterocyclic of pyrimidine β-lactam, thiazolidine and triazine derivatives incorporating benzpyrimidine derivatives have been synthesized by different method reactions (cycloaddition reaction, condensation reaction and cyclocondensation elimination reaction) of cinnamonitrile, aromatic aldehydes, chloroacetyl chloride, thioglycolic acid and nitroso compounds, respectively.

Keywords: Benzpyrimidine, pyrimidine, β-lactam, thiazolidine, triazine.

INTRODUCTION

Fused pyrrole, triazole and isolated β-lactams, thiazolidinones incorporating benzpyrimidines show a wide spectrum of biological activities and have been exhaustively reviewed, the synthesis of various types of benzpyrimidine which shows a wide range of biological activities. A rapid progress in the work on fused and isolated benzpyrimidines has given rise to a number of compounds exhibiting potent pharmacological actions like adenosine kinase inhibitory activity [1-3] and antibacterial [4]. In our pervious work we reported the synthesis 3-hydroxy-2-methyl quinazoline-4-one and benzpyrid-4-one-2-oxime [5, 6], however a different approach was undertaken in the present one. This basically consists in the reaction of hydrazine hydrate with 2-methylbenzoxazinone in order to obtain 3-amino-2-methyl benzpyrimidine-4-one (1). Examples of natural nitrogen heterocyclic are Rutaecararpine which possesses intrinsic diuretic, uterotonic and hypertensive [7] and Luotonine A3 which exhibits antitumor activity [8]. These natural compounds contain benzpyrimidine nuclei [9].

RESULTS AND DISCUSSION

A fusion of equimolar amounts of hydrazine hydrate and 2-methyl benzpyrimidin-4-one were refluxed for half an hour. After the reaction mixture was cooled precipitates was formed, wash by water and crystallized from water to give 3-amino-2-methyl benzpyrimidin-4-one (1). The structure of compound 1 was confirmed by elemental analysis (c.f. Table **1**) and the IR spectrum (γKBr) showed general absorption bands at 3370 – 3300 cm^{-1} (γC-NH_2) and at 1686 cm^{-1} (γC=O). ^{1}H NMR spectrum (DMSO) [10] of compound 1 showed signals at δ 11.05 ppm (br, 2H, NH_2), 8.4 – 6.8 ppm (m, 4H, ArH^+), 1.9 ppm (s, 3H, CH_3), (c.f. Table **2**). The mass spectrum [11] of compound 1 confirmed a molecular formula $C_9H_9N_3O$ agree with a molecular ion peaks at m/z = 175 and base peak at m/z = 117, (Equation **1**).

3-Amino2-methyl benzpyrimidin-4-one (1) was added to double bond in cinnamonitrile in refluxing ethanol as solvent and few drops of piperidine to yield corresponding pyrido benzpyrimidine derivatives (2a-d), (Equation **2**).

The first step in the previous mechanism involves formation of carbanion (a) using piperidine as catalyst which abstract a proton from active methyl group, accordingly it was added itself on the cinnamonitrile compound forming intermediate compound (b) uptake a proton from the piperidinium ion and lose a mole of hydrogen and hydrogen cyanide to produce the compound 2a-d.

The structure of compound 2a-d was confirmed by elemental analysis (c.f. Table **1**) and the IR spectrum (γKBr) showed general absorption bands at 3400 – 3200 cm^{-1} (γC-NH_2), 2220 cm^{-1} (γC≡N) and at 1660 cm-1 (γC=O). ^{1}H NMR spectrum (DMSO) [10] of compound 2a-d showed signals at δ 9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+ + CH olefin), 5(s, 2H, NH_2); 9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+), 2.6(q, 2H, CH_2), 1.3(t, 3H, CH_3); 9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+), 5(s, 2H, NH_2), 1.7(s, 3H, CH_3); 9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+), 2.5(q, 2H, CH_2), 1.2(t, 3H, CH_3), 1.5(s, 3H, CH_3), (c.f. Table **2**).

The mass spectrum [11] of compound 2a-d confirmed a molecular formula agrees with a molecular ion peaks (c.f. Table **2**). The high resolutions of mass spectrum of compound 2b as example confirmed a molecular formula $C_{21}H_{18}N_4O_2$ agrees with a molecular ion peaks at m/z = 358 (M = 2) and base peak at m/z = 303.

The amino benzpyrimidine derivatives 1 were condensed with different aromatic aldehydes in ethanol under piperidine as catalyst to yield the corresponding Schiff base derivatives 3a-e [12], (Equation **3**).

The first step in the previous mechanism involves formation of carbanion (a) using piperidine as catalyst, which abstract a proton from the active hydrogen center, accordingly it was added itself on the polarized aromatic aldehyde compounds forming the intermediate compound (b) uptake a proton from the piperidium ion forming compound (c). The latter compound (c) loses a mole of water to produce

*Address correspondence to this author at the Chemistry Department, Aswan Faculty of Science, South Valley University, Aswan, Egypt;
Tel: 0020972321986; Fax: 0020973480450;
E-mail: hsoleiman2001@yahoo.com

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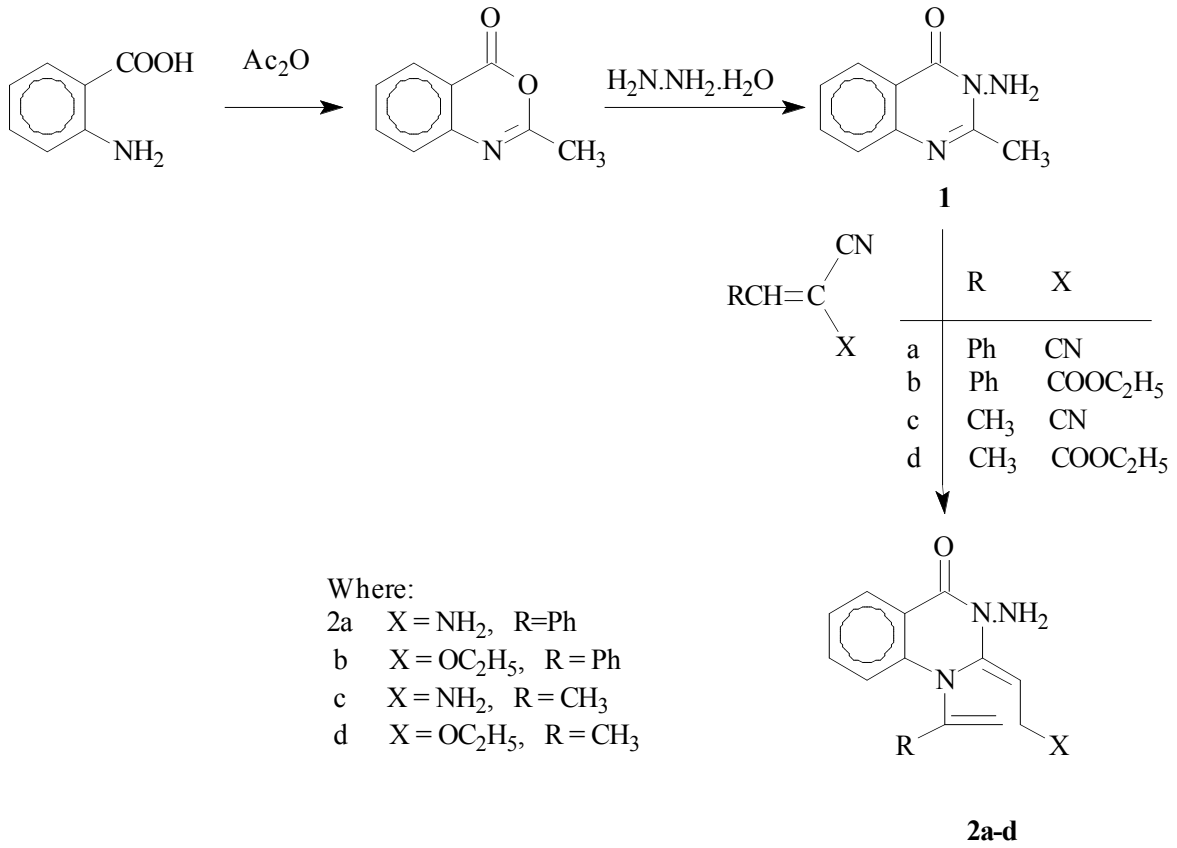
Table 1. Characterization of Compounds (1 – 6)

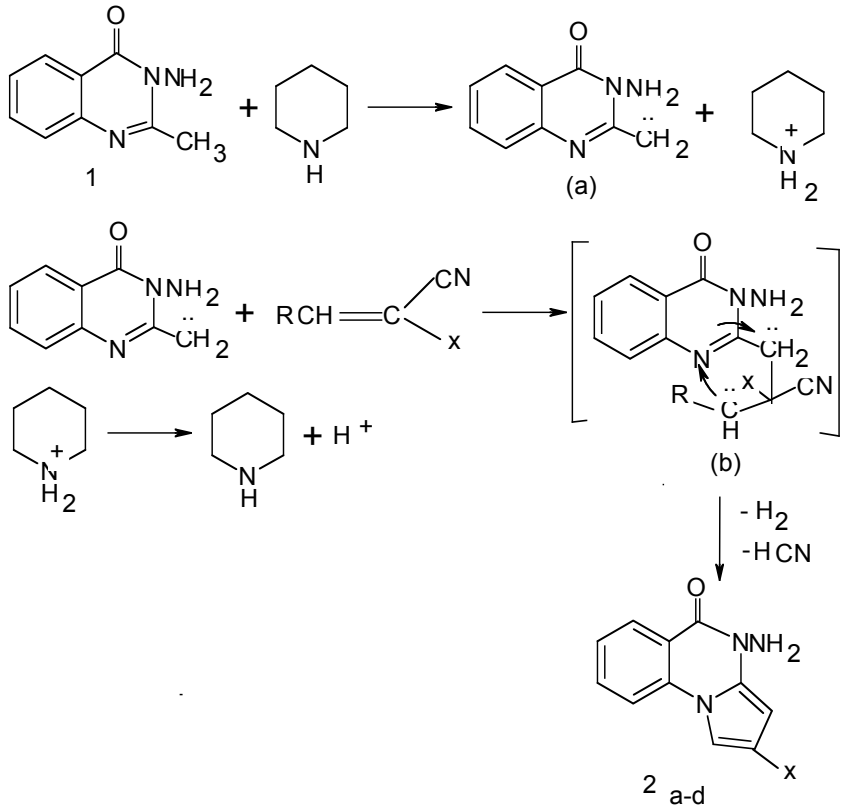
Comp. No.	M.P. °C	Colour	Yield %	(M. Wt.) M.F.	Analysis %			MS (m/z)
					C	H	N	
1	149-151	Pale yellow	90	$C_9H_9N_3O$ (175)	61.71 61.70	5.14 5.14	24.00 24.00	175
2a	192-195	Brownish yellow	12	$C_{19}H_{14}N_5O$ (342)	69.51 69.50	4.27 4.27	21.34 21.34	342
2b	95-98	White	80	$C_{21}H_{18}N_4O_2$ (358)	70.39 70.40	5.03 5.00	15.64 15.63	356
2c	144-146	Brown	21	$C_{14}H_{13}N_5O$ (267)	62.92 62.90	4.87 4.86	26.22 26.20	267
2d	140-142	Yellow	24	$C_{16}H_{16}N_4O_2$ (296)	64.86 64.86	5.40 5.40	18.92 18.90	296
3a	184-185	Pale yellow	53	$C_{16}H_{13}N_3O$ (263)	73.00 73.00	4.94 4.95	15.97 16.00	263
3b	260-262	Chine pale yellow	50	$C_{16}H_{13}N_3O_2$ (279)	68.82 68.80	4.66 4.65	15.05 15.02	279
3c	216-218	Pale yellow	63	$C_{16}H_{12}N_3OCl$ (297.5)	64.54 64.50	4.03 4.00	14.12 14.10	279
3d	194-196	Chine orange crystals	31	$C_{16}H_{18}N_4O$ (282)	68.08 68.10	6.38 6.40	19.86 19.85	280
3e	181-183	White	48	$C_{17}H_{15}N_3O_2$ (293)	69.62 69.60	5.12 5.12	14.33 14.35	293
4a	189-191	Pale yellow crystals	39	$C_{18}H_{14}N_3O_2Cl$ (339.5)	63.62 63.60	4.12 4.00	12.37 12.40	339
4b	265-267	White	38	$C_{18}H_{14}N_3O_3Cl$ (355.5)	60.76 60.74	3.94 3.94	11.81 11.80	355
4c	208-210	Yellow crystals	24	$C_{18}H_{13}N_3O_2Cl_2$ (374)	57.75 57.75	3.47 3.50	11.23 11.20	372
4d	187-189	Pale yellow	12	$C_{18}H_{19}N_4O_2Cl$ (465.5)	60.25 60.28	5.30 5.30	15.62 15.60	465
4e	180-182	Pale yellow	25	$C_{19}H_{16}N_3O_3Cl$ (369.5)	61.70 61.70	4.33 4.30	11.37 11.35	369
5a	196-198	Pale yellow crystals	48	$C_{18}H_{15}N_3O_2S$ (337)	64.09 64.10	4.45 4.45	12.46 12.45	337
5b	268-270	Pale yellow crystals	38	$C_{18}H_{15}N_3OS$ (353)	61.19 61.20	4.25 4.25	11.89 11.90	351
5c	204-206	Pale yellow	64	$C_{18}H_{14}N_3O_2ClS$ (371.5)	58.14 58.16	3.77 3.80	11.30 11.30	371
5d	189-191	Chine yellow crystals	25	$C_{18}H_{20}N_4O_2S$ (356)	60.67 60.65	5.62 5.60	15.73 15.75	354
5e	134-136	Yellow	80	$C_{19}H_{17}N_3O_3S$ (367)	62.12 62.10	4.63 4.60	11.44 11.00	366
6a	174-176	Yellow	20	$C_{18}H_{10}N_4O$ (298)	72.48 72.50	3.36 3.35	18.79 18.80	298
6b	145-147	Yellow	25	$C_{18}H_{10}N_4O$ (298)	72.48 72.50	3.36 3.35	18.79 18.80	298

the Schiff base compounds 3a-e (general scheme). The structure of compound 3a-e was confirmed by elemental analysis (c.f. Table **1**) and spectral analysis.

Thus, the IR spectrum (γKBr) showed general absorption bands at 3550 – 3500 cm^{-1} (γNH_2, OH), 1700 cm^{-1} (γC=O) and at 1600 cm^{-1} (γC=N).^{1}H NMR spectrum (DMSO) [10] of compound 3a-e showed signals at δ 8.5-6.5(m, 10H, Ar-H^+ + CH olefin), 1.7(s, 3H, CH_3); 9.9(s, 1H, OH), 8.5-6.5(m, 9H, Ar-H^+ + CH olefin), 1.9(s, 3H, CH_3); 8.3-6.6(m, 9H, Ar-H^+ + CH olefin), 1.5(s, 3H, CH_3); 8.5-7(m, 9H, Ar-H^+ + CH olefin), 2.2(s, 6H, N(CH_3)$_2$) 1.8(s, 3H, CH_3); 8-6.7(m, 9H, Ar-H^+ + CH olefin), 3.4(s, 3H, OCH_3) 1.6(s, 3H, CH_3), (c.f. Table **2**).



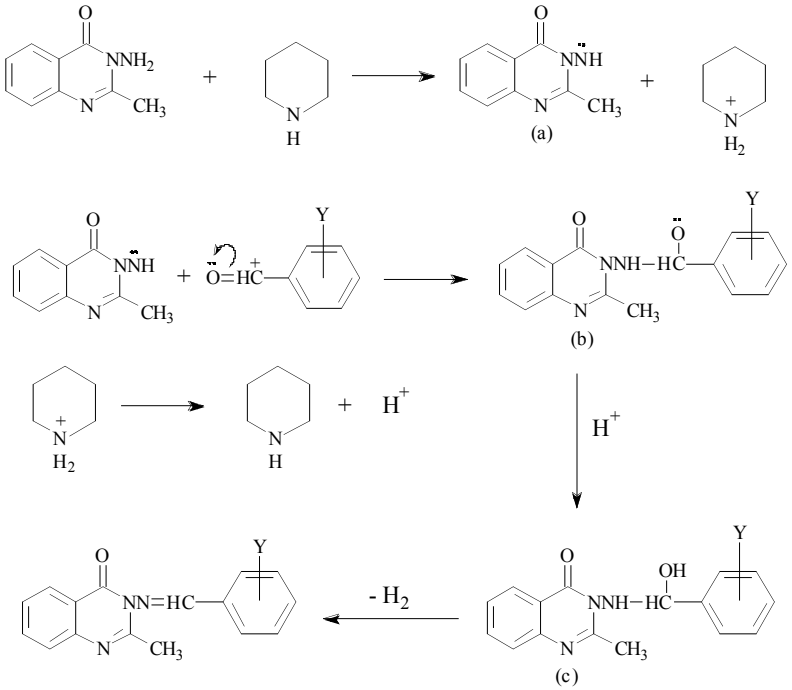
equation 1



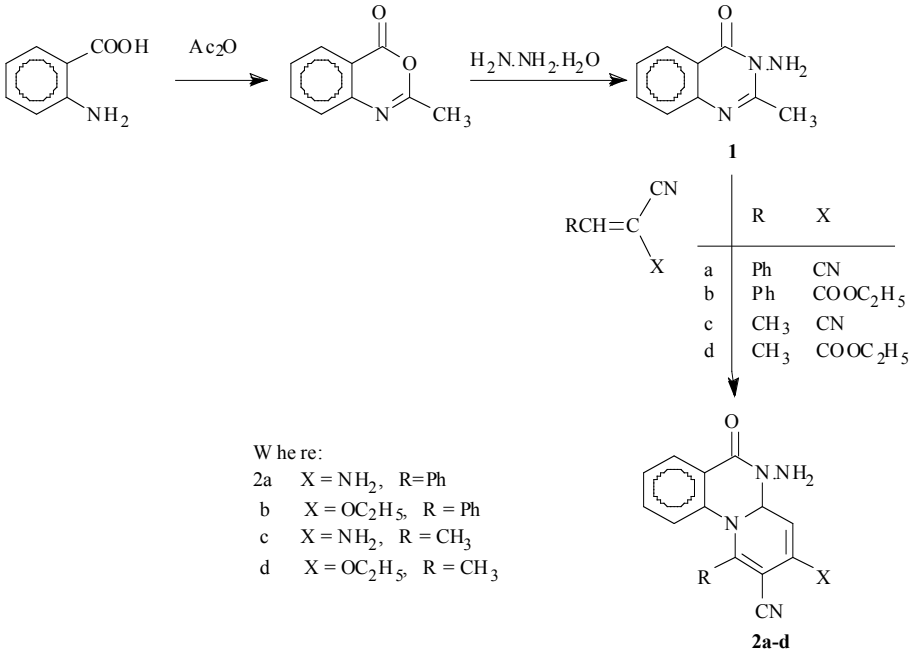
equation 2

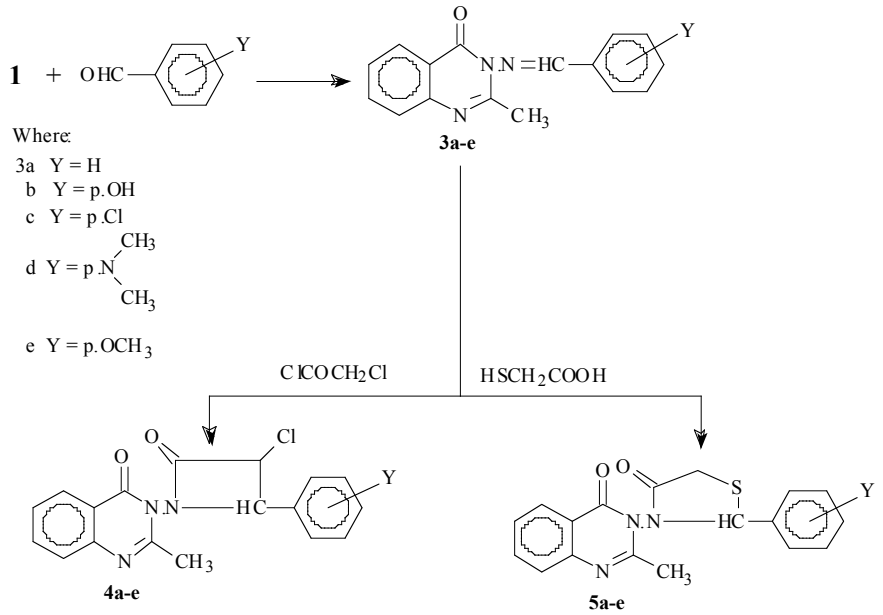
Table 2. ^{1}H NMR Spectral Data of Compound 2 – 5

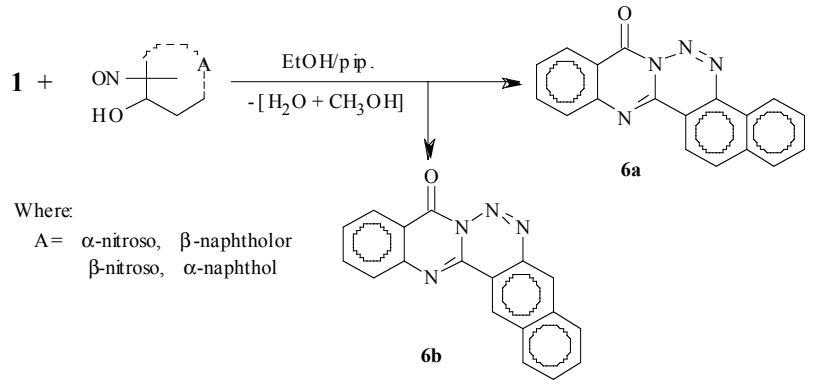
Comp. No.	^{1}H NMR (S ppm)
2a	9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+ + CH olefin), 5(s, 2H, NH_2).
2b	9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+), 2.6(q, 2H, CH_2), 1.3(t, 3H, CH_3).
2c	9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+), 5(s, 2H, NH_2), 1.7(s, 3H, CH_3).
2d	9(s, 2H, NH_2), 8.5-7(m, 10H, Ar-H^+), 2.5(q, 2H, CH_2), 1.2(t, 3H, CH_3), 1.5(s, 3H, CH_3).
3a	8.5-6.5(m, 10H, Ar-H^+ + CH olefin), 1.7(s, 3H, CH_3).
3b	9.9(s, 1H, OH), 8.5-6.5(m, 9H, Ar-H^+ + CH olefin), 1.9(s, 3H, CH_3).
3c	8.3-6.6(m, 9H, Ar-H^+ + CH olefin), 1.5(s, 3H, CH_3).
3d	8.5-7(m, 9H, Ar-H^+ + CH olefin), 2.2(s, 6H, $N(CH_3)_2$) 1.8(s, 3H, CH_3).
3e	8-6.7(m, 9H, Ar-H^+ + CH olefin), 3.4(s, 3H, OCH_3) 1.6(s, 3H, CH_3).
4a	8.2-6.8(m, 9H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH) 1.5(s, 3H, CH_3).
4b	9.5(s, 1H, OH), 8.6-7(m, 8H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH) 1.9(s, 3H, CH_3).
4c	8.5-7(m, 8H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH) 1.6(s, 3H, CH_3).
4d	8.7-7.2(m, 8H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH), 2.2(s, 6H, $N(CH_3)_2$), 1.9(s, 3H, CH_3).
4e	8.5-7(m, 8H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH), 3.4(s, 3H, OCH_3), 1.6(s, 3H, CH_3).
5a	8-6.7(m, 9H, Ar-H^+), 6.5(d, 1H, CH), 3.2(s, 2H, CH_2) 1.5(s, 3H, CH_3).
5b	9.7(s, 1H, OH), 8.5-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.2(s, 2H, CH_2) 1.9(s, 3H, CH_3).
5c	8.3-6.8(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.4(s, 2H, CH_2) 1.7(s, 3H, CH_3).
5d	8.5-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.3(s, 2H, CH_2), 2.2(s, 6H, $N(CH_3)_2$), 1.6(s, 3H, CH_3).
5e	8-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.6(s, 2H, CH_2), 3.4(s, 3H, OCH_3), 1.9(s, 3H, CH_3).
6a	8-7(m, 14H, Ar-H^+).
6b	8-7(m, 14H, Ar-H^+).



equation 3


COOH
Ac2O
NH2
H2N.NH2.H2O
N.NH2
CH3
1
RCH=C
CN
X
R X
a Ph CN
b Ph COOC2H5
c CH3 CN
d CH3 COOC2H5
Where:
2a X = NH2, R=Ph
b X = OC2H5, R = Ph
c X = NH2, R = CH3
d X = OC2H5, R = CH3
2a-d

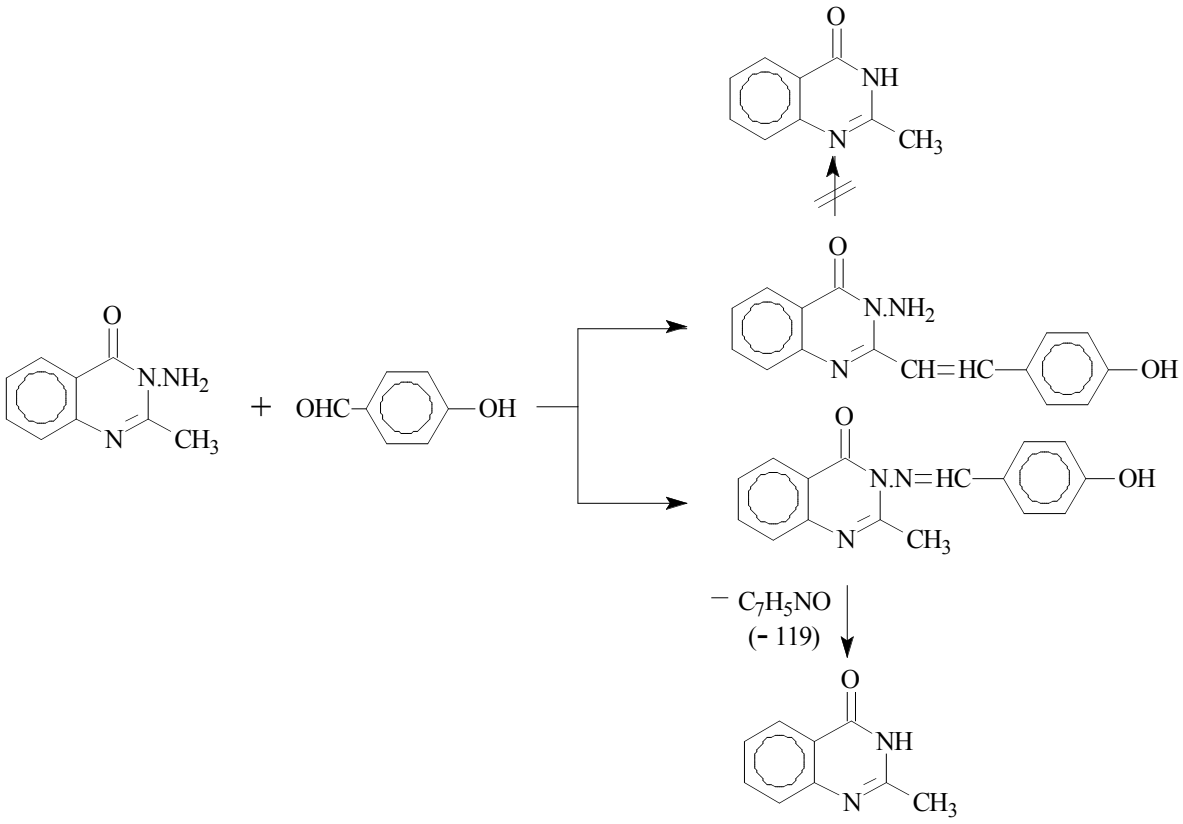

1 + OHC
Y
N.N=HC
CH3
3a-e
Where:
3a Y = H
b Y = p.OH
c Y = p.Cl
d Y = p.N(CH3)2
e Y = p.OCH3
ClCOCH2Cl
HSCH2COOH
Cl
S
4a-e
5a-e


1 +
ON
HO
A
EtOH/pip.
-[H2O + CH3OH]
6a
6b
Where:
A= α-nitroso, β-naphtholor
β-nitroso, α-naphthol

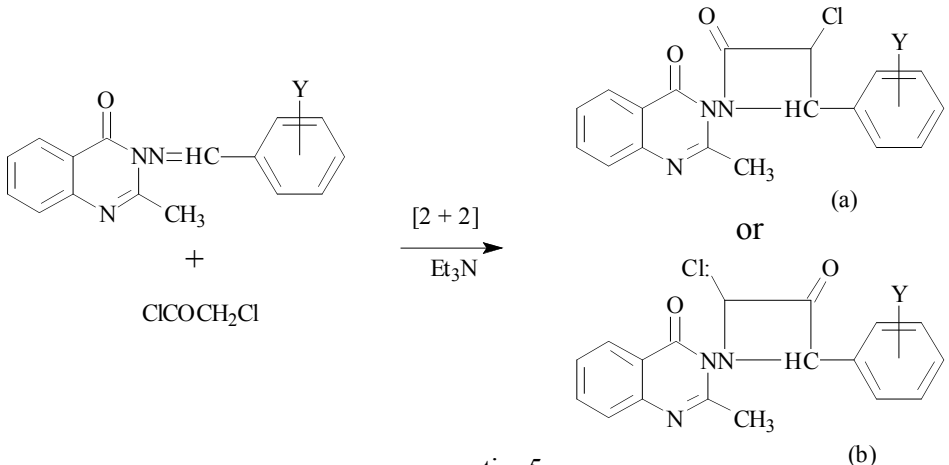
The mass spectrum [11] of compound 3a-e confirmed a molecular formula agrees with a molecular ion peaks (c.f. Table **2**). The mass spectrum of compound 2b as example confirmed a molecular formula $C_{16}H_{13}N_3O_2$ agrees with a molecular ion peaks at m/z = 279 and base peak at m/z = 160. The structure (b) was preferred over possible (a) base on the mass fragmentation with revealed base peak at m/z = 160, (Equation **4**).

The reaction of Schiff base derivatives 3a-c with equimolar ratios of chloroacetyl chloride afforded isolated β-lactam derivatives 4a-e [13] (general scheme). The cycloaddition proceeded smoothly of dioxane in the presence of triethylamine catalyst. The reaction of compound **2** with chloroacetyl chloride proceeded through [2+2] cycloaddition, the reactions are presented as follows, (Equation **5**).

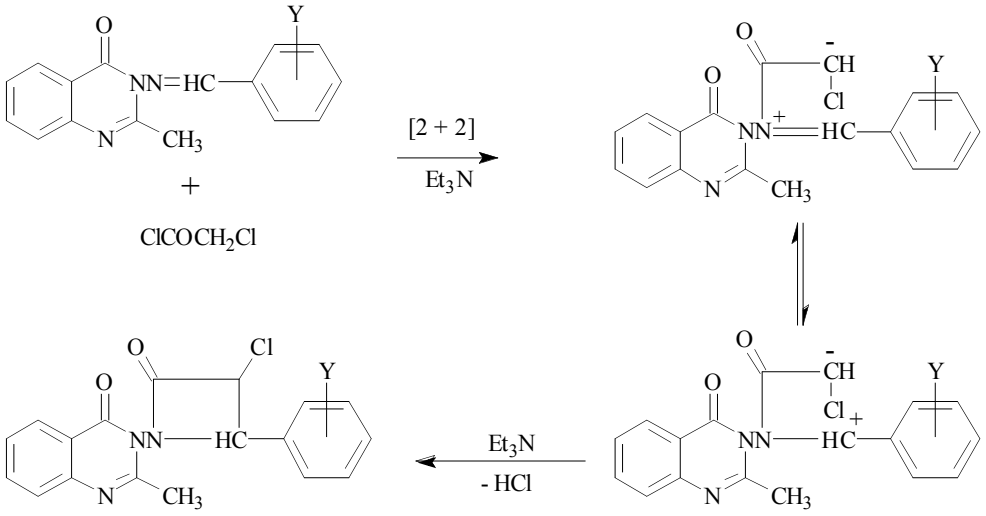
Structure (b) was preferred over possible (a) based on ^1H NMR which revealed proton b-lactam nuclei appeared at δ = 4ppm. The more stable product formed according to the following mechanism, (c.f. Equation **6**).



equation 4



equation 5



equation 6

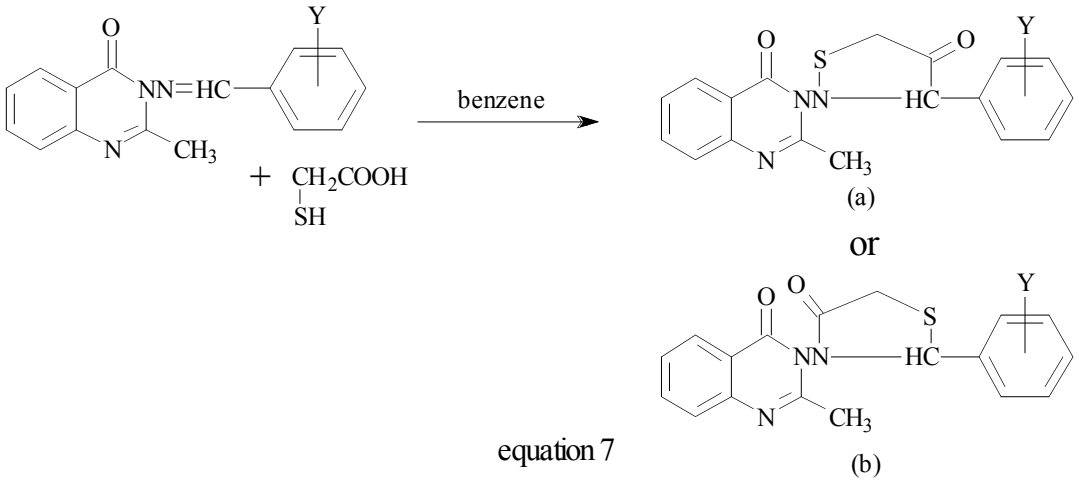
The structure of compound 4a-e was confirmed by elemental analysis (c.f. Table **1**) and spectral analysis. Thus, the IR spectrum (γKBr) showed general absorption bands at 3350 – 3300 cm^{-1} (γNH_2, OH), and at 1750 cm-1 (γC=O).^{1}H NMR spectrum (DMSO) [10] of compound 4a-e showed signals at δ 8.2-6.8(m, 9H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH) 1.5(s, 3H, CH_3); 9.5(s, 1H, OH), 8.6-7(m, 8H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH) 1.9(s, 3H, CH_3); 8.5-7(m, 8H, Ar-H^+), 3.6(d, 1H, CH), 3.4(d, 1H, CH) 1.6(s, 3H, CH_3); 8.5-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.3(s, 2H, CH_2), 2.2(s, 6H, $N(CH_3)_2$), 1.6(s, 3H, CH_3); 8-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.6(s, 2H, CH_2), 3.4(s, 3H, OCH_3), 1.9(s, 3H, CH_3), (c.f. Table **2**). The mass spectrum [11] of compound 4a-e confirmed a molecular formula agree with a molecular ion peaks (c.f. Table **2**).

Cycloaddition reaction of thioglycolic acid to the previously prepared Schiff base compound 3a-e proceeded successfully, afforded thiazolidinone derivatives 5a-e [13] as fellow, (Equation **7**).

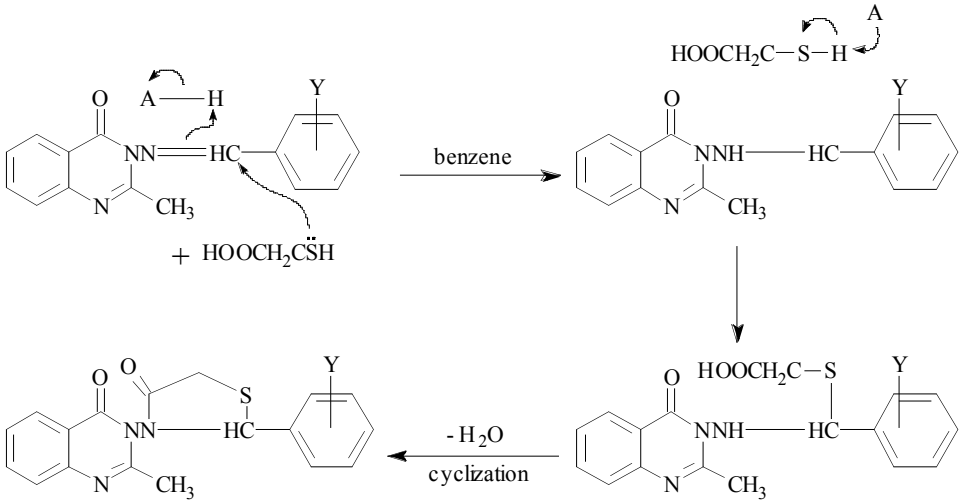
The cycloaddition reaction was assumed to go through the following suggested mechanism, (Equation **8**).

The structure of compound 5a-e was confirmed by elemental analysis (c.f. Table **1**) and spectral analysis. Thus, the IR spectrum (γKBr) showed general absorption bands at 3320 cm-1 (γOH) and at 1720 cm-1 (γC=O).^{1}H NMR spectrum (DMSO) [10] of compound 5a-c showed signals at δ 8-6.7(m, 9H, Ar-H^+), 6.5(d, 1H, CH), 3.2(s, 2H, CH_2) 1.5(s, 3H, CH_3); 9.7(s, 1H, OH), 8.5-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.2(s, 2H, CH_2) 1.9(s, 3H, CH_3); 8.3-6.8(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.4(s, 2H, CH_2) 1.7(s, 3H, CH_3); 8.5-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.3(s, 2H, CH_2), 2.2(s, 6H, $N(CH_3)_2$), 1.6(s, 3H, CH_3); 8-7(m, 8H, Ar-H^+), 6.5(s, 1H, CH), 3.6(s, 2H, CH_2), 3.4(s, 3H, OCH_3), 1.9(s, 3H, CH_3). (c.f. Table **2**). The mass spectrum [11] of compound 5a-e confirmed a molecular formula agree with a molecular ion peaks (c.f. Table **2**).

On the other hand, the condensed amino benzpyrimidine (1) with different nitroso compounds such a α-nitroso-β-naphthol and β-nitroso-α-naphthol gave triazino benzpyrimidine derivatives 6a, b, the structure of triazino compound derivatives (6a, b) was confirmed by elemental analysis (c.f. Table **1**) and spectral analysis. Thus, the IR spectrum (γKBr) showed general absorption bands at 1700



equation 7



equation 8

cm-1 (γC=O) and 1600 cm-1 (γC=N).^{1}H NMR spectrum (DMSO) [10] of compound 6a, b showed signals at δ 8 – 7 (m, 10, ArH^+) (c.f. Table **2**). The mass spectrum [11] of compound 6a, b confirmed a molecular formula agrees with a molecular ion peak at m/z = 299.

EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded on a Pye Unicam SP 1100 Spectrophotometer using KBr disc. ^{1}H NMR spectra were recorded on a Varian EM – 390 MHz spectrophotometer using DMSO d_6 as a solvent and TMS as an internal standard. Chemical shifts are expressed as ppm, units. Mass spectra were recorded on an HP Ms 6988 spectrometer. Analytical data were determined with a CE 440 Elemental Analyzer-Automatic Injector at Cairo University.

Synthesis of 3-Amino-2-Methylbenzpyrimidin-4-One (1)

General Procedure

A mixture of 2-methyl benzpyrimidin-4-one (1.6 g, 0.01 moles) and hydrazine hydrate (0.50 ml, 0.01 moles) were fused for half an hour. A pale yellow precipitate formed was washed several times with water. It was crystallized from water to give compound 1.

Synthesis of Pyrido [1, 2-a] Benzpyrimidine Derivatives 2a-d

General Procedure

Equimolar amounts of compound 1 and ylidene cinnamonitrile (0.01 moles) in ethanol (50 ml) were treated with a few drops of piperidine. The reaction mixture was refluxed for 2 hours, then left to cool. The solid product so formed was separated by filtration and crystallized from ethanol to yield compound 2a-d.

Synthesis of 3-Azarylbenzpyrimidine Derivatives 3a-e

General Procedure

Compound 1 (0.01 mole) and aromatic aldehydes (0.01 mole) in equimolar ratio were dissolved in ethanol and few drops of piperidine as catalyst were added, the reaction mixture was refluxed about 6-8 hours. The solid product so formed was separated by filtration and crystallized from ethanol to yield compound 3a-e.

Synthesis of β-Lactam Benzpyrimidine Derivatives 4a-e

General Procedure

To a well stirred solution (0.01 mole) of base (3a-e) and (0.02 mole) of triethylamine in 100 mls of dry dioxane were added (0.02 mole) of monochloroacetyl chloride drop wise at room temperature. The mixture is stirred for extra 9 hours, and left at room temperature for 3 days. The formed precipitate (triethylamine hydrochloride) was filtered off, washed thoroughly with the same solvent (dioxane). The combined solvent and filtrate, washed thoroughly with dilute hydrochloric acid three times then water, then dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated under reduce pressure. The residue was collected and purified to yield compound 4a-e.

Synthesis of Thiazolbenzpyrimidine Derivatives 5a-e

General Procedure

A mixture of equimolecular amount of Schiff bases 3a-e (0.01 moles) and thioglycolic acid in 100 ml dry benzene was refluxed with water, and separated until the theoretical amount of water had been removed. The solid product so formed was collected and crystallized from ethanol to yield 5a-e.

Synthesis of Triazinobenzpyrimidine Derivatives 6a, b

General Procedure

Equimolar amounts of compound 1 and α-nitroso-β-naphthol or β-nitroso-α-naphthol (0.01 moles) were dissolved in ethanol as organic solvent under a few drops of piperidine as catalyst. The reaction mixture was refluxed about 5-6 hours. The solid product so formed was separated by filtration and crystallized from ethanol to yield compound 6a, b.

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