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Synthesis and biological activities of some new fully fused quinazoline derivatives

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Some fully fused quinazoline derivatives have been synthesized via condensation of 3-formylpyrazolo[5,1-*b*]quinazolin-9(1*H*)one **2** with bifunctional reagents followed by ring closure reactions. The structures of the products have been established by their elemental analyses and spectral data (UV, IR, ^{1}H NMR, mass and X-ray). The antibacterial activity of some products have been also described. Compounds **7, 12b** and **13** show a relatively better activity against some tested bacteria in comparison with gentamycin.

4-Quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs[1,2]. Furthermore, many fused quinazolinones are found to exhibited remarkable pharmacological agents[3-7]. In search for new antimicrobial agents, it was thought worthwhile to incorporate some additional heterocyclic moieties in the quinazoline nucleus and study their biological activity via the interaction between formylpyrazoloquinazolinone **2** with nitrogen and oxygen compounds. The starting compound 3-formylpyrazolo[5,1-*b*]quina-zolin-9(1*H*)one **2**[8] was obtained from formylation of 3-amino-2-methylquinazolin-4-one **1** by treatment with DMF-$POCl_3$ [Vilsmeier-Haak reagent].

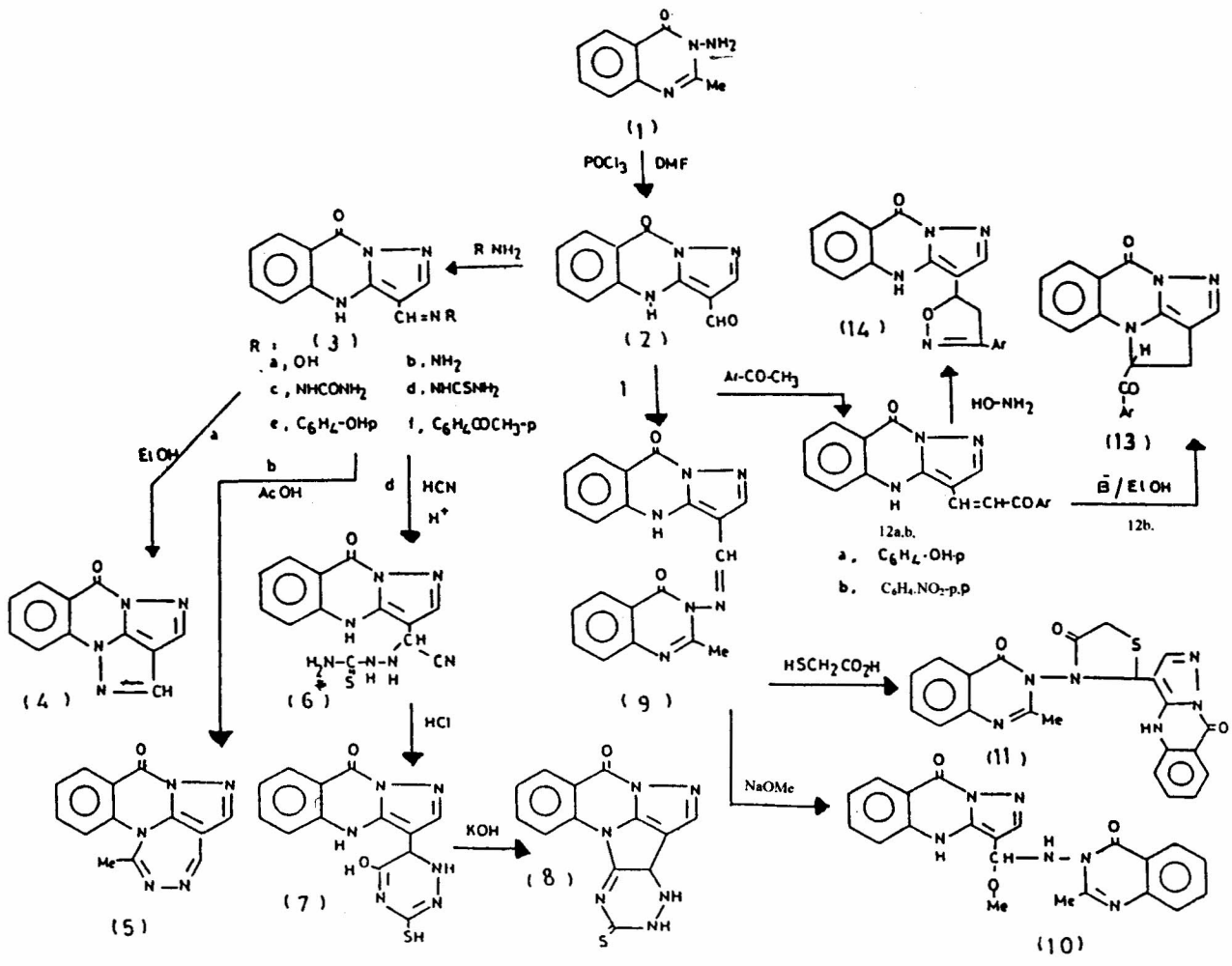
Condensation of **2** with hydroxylamine hydrochloride, hydrazine hydrate, semicarbazide hydrochloride, thiosemicarbazide, 4-aminophenol and 4-aminoacetophenone refluxing in ethanol, produced **3a-f** (Scheme I). Structure of **3** was established from elemental analyses and spectral data (Table I). IR spectrum of **3e** showed bands due to NH-OH, C=O and exo, endo CH=N functional groups. Its UV spectrum revealed the presence of absorption band at λ_{max} 305, 349 and 485 nm in the visible region. These bands reported the π^* electron transition and the charge transfer band respectively.

The greater reactivity of the hydrogen atom of the NH of quinazolinone **2** is presumably due to its favourable location between two carbonyl functions in position 9 and CHO group in the position 3 of pyrazoloquinazolinone. Thus, cyclization of **3a** by refluxing in abs. ethanol-fused sodium acetate[9] yielded quinazolino[1,2-*b*:2,3-*b*]dipyrazolo-10-one **4**, while attempts to the cyclization of **3b** using gl. acetic acid-fused sodium acetate afforded 6-methyl-1,2,4-triazino[5,6:4,5]pyrazolo[5,1:2,3']quinazololin-12- one **5**.

The structures **4** and **5** were preferred on the following grounds: i) absence of NH or OH absorption bands in the IR spectra, ii) the presence of only one C=O absorption band at 1677 cm^{-1}.

On the other hand addition of HCN to thiosemicarbazone **3d** in the presence of gl. acetic acid-ethanol[10] afforded 4*H*-3(α-cyano-α-thiosemicarbazido)methylpyrazolo[5,1-*b*]quinazolin-9-one **6**, which on boiling with conc. HCl furnished[10] 6-[(4H)pyrazolo[5, 1-*b*]quinazolin-9-one-3-yl]-1, 6-dihydro-3-mercapto-1,2,4-triazin-5(4*H*)one **7**, while basic cyclization of 7 by refluxing with aq. KOH[4] produced 3*H*-5-mercapto-1,2,4-triazino[5',6' : 2,3]-[4,5-*c* :1,5-*a*]pyrazolo-quinazolin-12-one **8** (Scheme I).

Structure of compounds **6-8** was confirmed from their elemental analyses and spectral data (Table I). Their IR spectra showed characteristic bands at 2700 (SH) and 1200-1100 cm^{-1} (C-S) with disappearance of band at 2300-2200 cm^{-1} (CN) in **7** and **8** while IR spectra of **6** and **8** revealed only one absorption band at 1693 cm^{-1} due to cyclic C=O of quinazolinone and a broad band at 3300-3100 cm^{-1} was observed in case of **7** and **8** due to cyclic



Scheme I

hydrazo structure. In addition, structure assigned to **8** was verified from ^{1}H NMR spectrum which showed signals at δ 2.8 (s, 1H, of pyrole moiety), 7.5-8.5 (m, 5H, benzo protons of quinazoline and CH of pyrazole moiety), 10.1 (s, 1H, SH), 10.4 and 11.0 ppm (each singlet for NH of 1,2,4-triazine).

Conversion of **6** to **8** was established via acidic hydrolysis of cyano group to carboxylic group followed by cyclization and then elimination of a molecule of water by refluxing with aq. KOH.

Condensation of **1** with **2** gave the Schiff base **9** which on refluxing with sodium methoxide afforded the adduct **10**. Reaction of arylidine **9** with mercaptoacetic acid in dry dioxane-fused sodium sulphate yielded the thiazolidin-4-one **11** (Scheme I).

Structures of **10** and **11** were deduced from elemental analyses and IR spectral data. Compound **10** revealed absorption bands in the IR spectrum region due to C=O and C-O-R, while that of **11** exhibited absorption bands at 3120 (NH of quinazoline), 2880 (aliphatic CH), 1740, 1700, 1680 (3 C=O of quinazoline and thiazolidine-4-one)[11].

On the other hand, condensation of 3-formylpyrazolo[5,1-*b*]quinazolin-9-(1*H*) one **2** with acetophenone derivatives in gl. acetic acid, afforded the chalcones **12 a,b**. Cycloaddition reaction of **12 a,b** by boiling with ethanol in the presence of a few drops of piperidine[12] gave heterotricyclic moiety **13**. The chemical transformation of **12** to **13** is outlined in Chart 1.

Structures of **12 a,b** were deduced from their elemental analyses and spectral data. Their IR spectra showed absorption bands at 3190 (NH of quinazoline), 3067 (aromatic CH), 2926 (aliphatic CH), 1690 (C=O), 1601 (C=C), 1573 cm^{-1} (C=N); ^{1}H NMR spectrum of **12b** revealed the presence of signals at 6.8-7.1 (m, 2H, –CH-CH–), 7.4-8.5 (m,

8H, pyrazolo & aromatic protons) and 8.8 (s, 1H, NH). UV spectrum of **12b** in DMF displayed λ_{max} at 526 nm with fluorescence in UV light, as possible fluorescent brighteners for synthetic fibres and plastics.

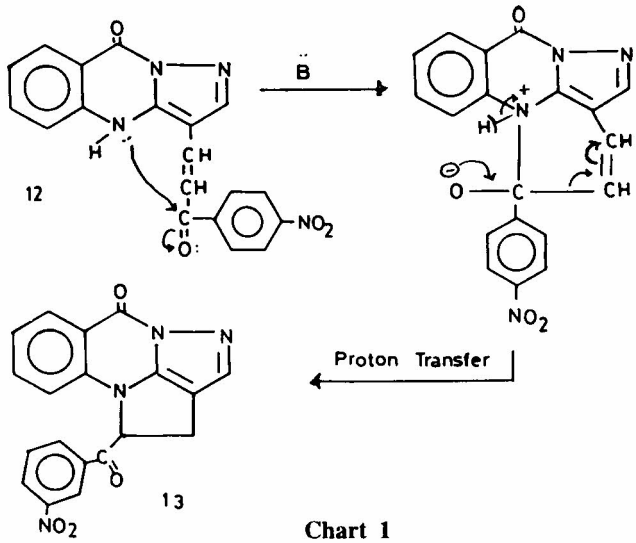


Chart 1

Refluxing compound **12b** in ethanol with a few drops of piperidine afforded compound **13**. Its structure was established on the basis of elemental analyses and spectral data. IR spectrum of it showed absorption bands at 1694, 1660 (2 C=O), 2900, 1490 (str. and def. CH_2) and 1530, 1320 cm^{-1} (asy. and sy. NO_2) with absence of a band due to OH or NH groups. Finally the structure of **13** was confirmed from mass spectra which showed a molecular ion peak at m/z 360 (1.23%), a base peak at m/z 150 (100%) attributed to p-nitrobenzoyl ion and under further fragmentation arrived to benzyene radical at m/z 76 (28.6%). All fragmentation paths leading to various daughter ions deduced the postulated structure (Chart II). In addition, compound **13** did not give phenolic test with $FeCl_3$ solution.

α,β-Unsaturated ketones **12 a,b** reacted with hydroxylamine hydrochloride in the presence of pyridine via Michael addition reaction to give isoxazole derivatives **14 a,b**. Structures of these products were elucidated by spectroscopic analyses. Thus, IR spectra of **14a** and **14b** showed absorptions

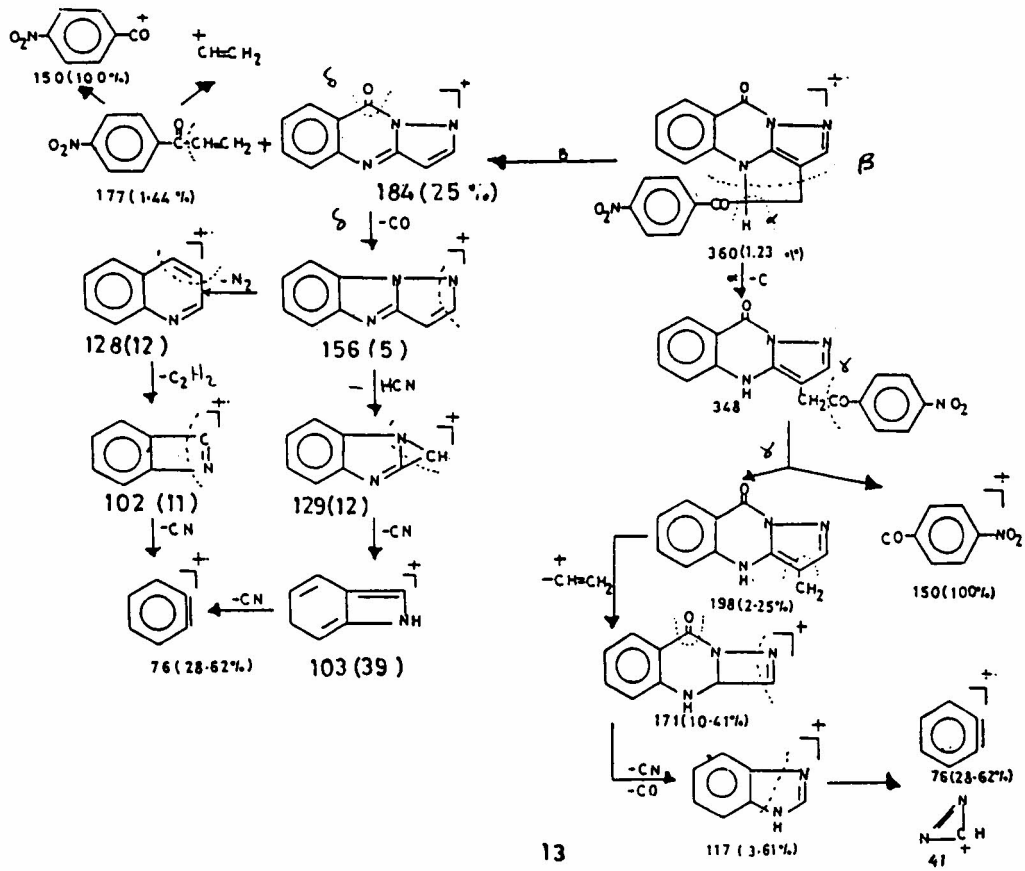


Chart 2

Table I—Physical and spectral data of the compounds **3-14**

Compd.	Solvent	M.P. (°C)	Yield %	Mol. formula* (M. wt.)	IR (cm^{-1}) OH	NH	SH	CO	C=N	C-S	C-O-R
3a	EtOH	155	80	$C_{11}H_8N_4O_2$ (228)	3500	3090	—	1670	1600	—	—
3b	EtOH	295	75	$C_{11}H_9N_5O$ (227)	—	3200	—	1675	1610	—	—
3c	EtOH	300	100	$C_{12}H_{10}N_6O_2$ (270)	3300	3100	—	1680	1620	—	—
3d	EtOH	280	76	$C_{12}H_{10}N_6OS$ (286)	—	3200	2700	1670	1590	1190	—
3e	EtOH	280	90	$C_{17}H_{13}N_4O_2$ (305)	3193	3080	—	1649	1608	—	—
3f	EtOH	238	88	$C_{19}H_{15}N_4O_2$ (331)	—	3100	—	1675 1700	1610 1580	—	—
4	EtOH	270	75	$C_{11}H_6N_4O$ (210)	—	—	—	1677	1590	—	—
5	EtOH	295	70	$C_{13}H_9N_5O$ (251)	—	—	—	1670	1580	—	—
6	Dil. DMF	290	84	$C_{13}H_{11}N_7OS$ (313)	—	3100	—	1680	1590	1200	—
7.	Dil DMF	300	95	$C_{13}H_{10}N_6O_2S$ (314)	3550	3300	2650	1680	1590 1610	1190	—
8	Dil. DMF	300	66	$C_{13}H_8N_6OS$ (296)	—	3300	—	1693	1580 1600	1200	—
9	DMF	300	90	$C_{20}H_{14}N_6O_2$ (370)	—	3090	—	1670 1700	1570 1600	1175	—
10	DMF	300	75	$C_{21}H_{18}N_6O_3$ (402)	—	3120	—	1680 1700	1590	—	1050
11	DMF	143	70	$C_{22}H_{16}N_6O_3S$ (444)	3300	—	—	1680 1700	1580 1610	1185	—
12a	DMF	265	50	$C_{19}H_{13}N_3O_3$ (331)	3400	3190	—	1680	1590	—	—
12b	DMF	225	100	$C_{19}H_{12}N_4O_4$ (360)	—	3180	—	1690	1573	—	—
13	Dil. DMF	275	80	$C_{19}H_{12}N_4O_4$ (360)	—	—	—	1694 1660	1590	—	—
14a	DMF	300	60	$C_{19}H_{14}N_4O_3$ (346)	—	3150	—	1680	1580	—	1050
14b	DMF	270	75	$C_{19}H_{13}N_5O_4$ (375)	—	3100	—	1675	1590	—	1060

*All the compounds gave satisfactory of C, H, and N analyses. Sulfer element has been determined by X-ray analyses: **3d**: Found 10.62; Calcd 11.18%; **6**: Found 9.61; Calcd 10.22%; **7**: Found 9.78; Calcd 10.19%; **8**: Found 9.99; Calcd 10.81%; **11**: Found 6.80; Calcd 7.20%.

W (DMF, λ_{max} nm): **3e**: 305, 349, 485; **12b**: 526; **14b**: 339, 526.

^{1}H NMR (DMSO) δ:**8**: 2.8 (1H of pyroles), 3.1 (H of pyrazole), 7.5-8.5 (14H benzo of quinazoline), 10.1 (1H, SH), 10.4 and 11.0 (each 1H, NH of 1,2,4-triazine); **12b**: 1.5 (3H, CH_3), 3.5 (1H, pyrazole), 7.5-7.7 (2H, CH=CH), 7.8-8.1 (4H, aromatic), 8.2-8.7 (4H, benzo) and 8.9 (1H, NH).

which are correlated to the NH_1 CH_2, C=O and C-O-N stretching frequencies of these compounds. The electronic spectra of these led further support to the proposed structure where they lack the absorption bands due to extended conjugation.

Antimicrobial activities. Compounds **3-13** have been tested for their antimicrobial evaluation against *S. aures, S. marcescens, B. subtilis, C, albine, E. coli* and *M. lutea* by the disc method[13] using DMF as solvent and gentamycin was used as standard at three different concentration (100, 500, and 1000 μg/ml) and growth inhibition was calculated.

The results showed that compounds **8** and **13** were active against *E. coli*, while compounds **6, 7**

Table II—Antimicrobial activities of the compounds 3-13

Compd*	*S. aures*	*S. marcescencs*	*B. subtilis*	*C. albine*	*E. coli*	*M. lutea*
3a	—	—	—	—	—	—
3b	—	—	—	—	—	—
3c	10	11	9	9	8	8
3d	12	14	10	8	10	7
3e	14	15	12	11	12	11
3f	—	—	—	—	—	—
4	—	—	—	—	—	—
5	—	—	—	—	—	—
6	14	15	17	12	10	12
7	16	13	15	11	11	12
8	—	—	24	—	23	20
9	—	—	—	—	—	—
10	—	—	—	—	—	—
11	15	—	—	—	—	—
12b	16	14	14	11	8	6
13	17	16	15	12	21	10
14	—	—	—	—	—	—
Gentamycin	23	23	24	23	23	20

*Diameter of inhibition zones

and **8** were active against *S. aures, S. lutes* and *B. subtilis*. All other compounds, exhibited varying degree (20-30%) of the antimicrobial activity. Compound **8** which was substituted with thioxo-1,2,4-triazine moiety to the pyrazoloquinazolinone showed maximum activity (38%). When phenyl ring was substituted with nitro group (at position-4), compound **13** showed maximum activity (34%), while both compounds **6** and **7** containing thiosemicarbazide and/or 3-mercapto-5-hydroxy-1,2,4-triazine moiety exhibited greater degree of inhibition when compared with other tested compounds (Table II). In conclusion, the compounds which contain the mercapto-1,2,4-triazine moiety, enhanced the inhibition percentage of the tested organisms.

Experimental Section

Melting points are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 293 FT spectrophotometer (λ_{max} in cm^{-1}), UV spectra (in DMF) on a LASTACQU. MRD (300-400) test spectrophotomer (λ_{max} in nm), ^1H NMR spectra on a EM NMR spectrometer 200 MH_z PMR using DMSO and/or acetone as a solvent and TMS as internal reference (chemical shifts in δ, ppm) and mass spectra on GCMS qp 1000 ex Schemimadzu instrument (70 eV). X-ray measurement were recorded in X-ray phosphorescences. Elemental analysis were performed on a Perkin-Elmer CHN 240A analyzer in unite, Cairo University (ARE).

Synthesis of condensation derivatives 3 a-f: General method. A suspension of **2** (10 m. mol)[8] in ethanol (50 mL) and the appropriate amino compounds namely hydroxylamine hydrochloride (in H_2O), hydrazine hydrate, semicarbazide (in H_2O), thiosemicarbazide (in hot water, drops of acetic acid), *p*-aminophenol and *p*-amino-acetophenone (each 10 m. mol) was refluxed for 1h, cooled and poured onto ice. The solid thus obtained was crystallized from the suitable solvent to give **3 a-f** (Table I).

Synthesis of quinazolino[1,2-*b* : 3,2-*b*]dipyrazolo-10-one 4. A suspention of 3a (10 mmol) in abs. ethanol (50 mL) and fused sodium acetate (5g) was heated under reflux for 4h, cooled and poured onto ice. The resultant solid was crystallized to give **4** (Table I).

Cyclization of 3b into heterotricyclic compound 5. A solution of **3b** (10 mmol) in gl acetic acid (100 mL) and fused sodium acetate (5 g) was refluxed for 2 h, cooled and poured onto ice. The solid obtained was filtered off and recrystallized to give **5** (Table I).

Synthesis of 4H-3-(α-cyano-α-thiosemicarbazido)methyl-pyrazolo[5,1-*b*]quinazolin-9-one 6. To **3d** (5 mmol) in ethyl alcohol (50 mL) and gl acetic acid (50 mL), aq solution of sodium cyanide

(5 mmol in H_2O 5 mL) was added. The reaction mixture was refluxed for 6 h, cooled and poured onto ice. The solid obtained was filtered off and recrystallized to give **6** (Table I).

Acidic hydrolysis of 6:Synthesis of 6-(4*H*-pyrazolo[5, 1-*b*]quinazolin-9-one-3-yl)-1, 6-dihydro-3-mercapto-1,2,4-triazin-5(4H)one 7. To **6** (5 mmol), HCl (20%, 20 mL) was added and the reaction mixture was refluxed for 10 h. The solid product was filtered off and recrystallized to give **7** (Table I).

Basic cyclization of 7:Synthesis of 3*H*-5-mercapto-1, 2, 4-triazino[5,6 : 2,3][4, 5- *c* : 1, 5-*a*]pyra-zoloquinazolin-12-one 8. To **7** (5 mmol), aq KOH (5%, 20 mL) was added and the reaction mixture was refluxed for 10 h. The solid obtained was recrystallized to give **8** (Table I).

Preparation of Schif's base 9. A mixture of **2** (10 mmol) and compound **1** (10 mmol) in gl acetic acid (50 mL) was heated under reflux for 2 h, cooled and poured onto ice. The resulting solid was crystallized to give **9** (Table I).

Addition of sodium methoxide to 9: Formation of 10. A suspention of **9** (0.5 g) in sodium methoxide (0.5 g Na in 50 mL abs ethanol) was refluxed for 12 h, cooled and poured onto ice-HCl. the solid obtained was recrystallized to give the adduct **10** (Table I).

Cycloaddition of 9 with thioglycolic acid: Formation of thiazolidinone 11. A mixture of **9** (10 m.mol) and mercaptoacetic acid (50 m. mol) in dioxan (100 mL) was refluxed for 8 h. The excess solvent was removed and the resulting solid mass was crystallized to give **11** (Table I).

Preparation of chalcones 12a and 12b. Equimolar mixture of **2** (10 mmol), the appropriate acetophenones namely, 4-hydroxyacetophenone, p-nitroacetophenone (10 mmol each) and acetic acid (3.3 mL), piperidine (0.5 mL) in benzene (100 mL) was refluxed for 24 h. The solid obtained was filtered off and recrystallized from the proper solvent to give **12a,b** (Table I).

Synthesis of heterotricyclic system 13. A mixture of **12b** (0.5 g), ethanol (50 mL), and piperidine (0.5 mL) was refluxed for 10 h. The solid obtained was filtered off and recrystallized to give **13** (Table I).

Synthesis of isoxazole derivatives 14a,b. A mixture of **12a,b** (10 mmol) and hydroxylamine hydrochloride (10 mmol in H_2O 5 mL), in pyridine (50 mL) was refluxed for 6 h, cooled, and poured onto ice-HCl. The solid obtained was filtered off and recrystallized to give **14** (Table I).

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