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A FACILE ONE-POT SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF AZIRIDINES AND THIAZINES FROM 1,3-DIARYLPROP-2-ENONES

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A FACILE ONE-POT SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF AZIRIDINES AND THIAZINES FROM 1,3-DIARYLPROP-2-ENONES

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The title compounds **1a,b** as examples for acyclic alkenones were utilized for the synthesis of some heterocycles namely, thiazines **2a,b** and **3a-d**, pyrimidines **4a,b**, aziridines **7a,b**. The unexpected tribromides **8a,b**, obtained from bromination of **1a,b**, were readily used to afford the pyrazoles **9a,b** and isoxazoles **10 a,b**. Biological screening of some selective synthesised compounds was determined in vitro using Gram-negative and Gram-positive bacterial strains.

The present work is a continuation of our publication[1] devoted to the synthesis of new heterocycles with the aim to investigate their biological activities. The synthetic goal of the present work was to obtain new heterocyclic systems from readily obtainable simple compounds viz. 1,3-diarylprop-2-enones **1a,b**.

The addition of thiourea, as an ambident nucleophile, to acyclic alkenones in presence of sodium alkoxide is a point of argument among synthetic organic chemists. Takamizawa et al.[2,3], Behringer et al.[4] and Mirskova et al.[5] have found that the reaction provides a synthetic route for thiazines. On the other hand, El-Hashash et al.[6,7] have isolated pyrimidine-2-thione derivatives.

This situation prompted us to reinvestigate the reaction of thiourea with α,β-ethylenic acyclic ketones. When the 1,3-diarylpropenones **1a,b** were allowed to react with thiourea in refluxing absolute ethanol in the presence

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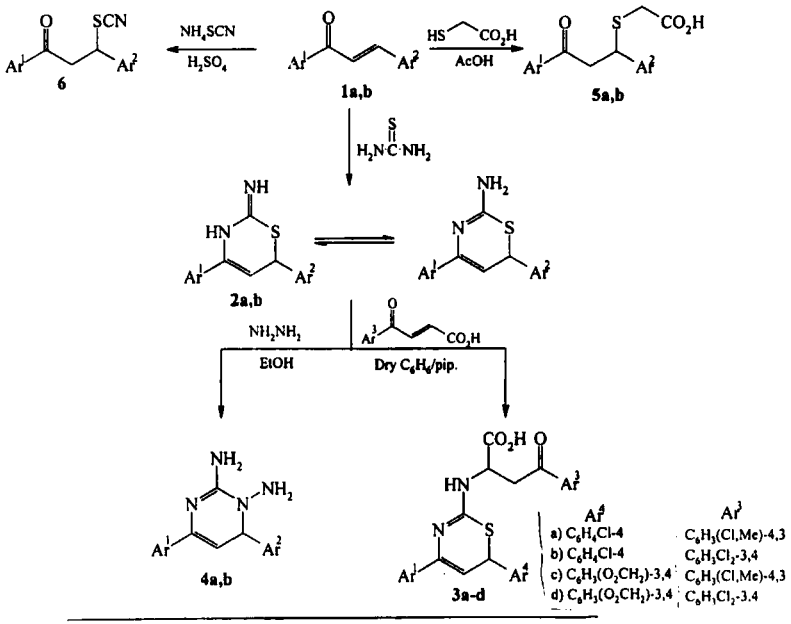
of sodium ethoxide only the diarylthiazines **2a,b** were isolated (cf. Scheme 1).When thiazines **2a,b** were subjected to the reaction with β-(4-chloro-3-methylbenzoyl)acrylic acid or β-(3,4-dichlorobenzoyl) acrylic acid in dry benzene containing a catalytic amount of piperidine, the products obtained were identified to be the corresponding γ-keto acids **3a-d** (cf. Scheme 1). Evidence for the proposed structures **3a-d** is due the positive acidity and the negative unsaturation tests together with their spectroscopic data (cf. Table II).



6 **1a,b** **5a,b** **2a,b** **4a,b** **3a-d**

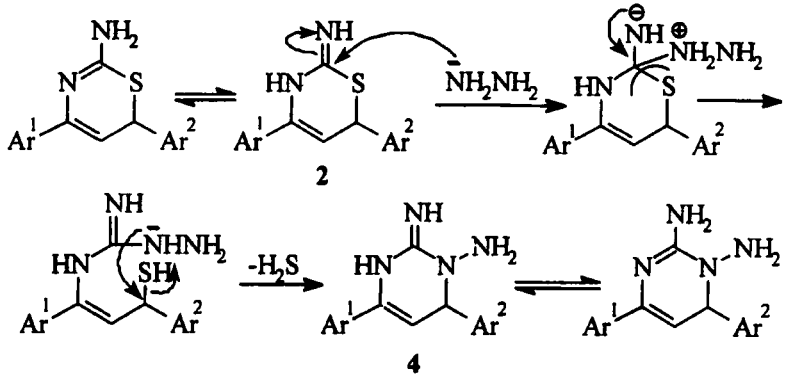
Ar^1 = $C_6H_3(OMe)_2$-2,4; Ar^2, a = C_6H_4Cl-4; b = $C_6H_3(O_2CH_2)$-3,4

The definitions of Ar^1 and Ar^2 are hold throughout the paper.

SCHEME 1

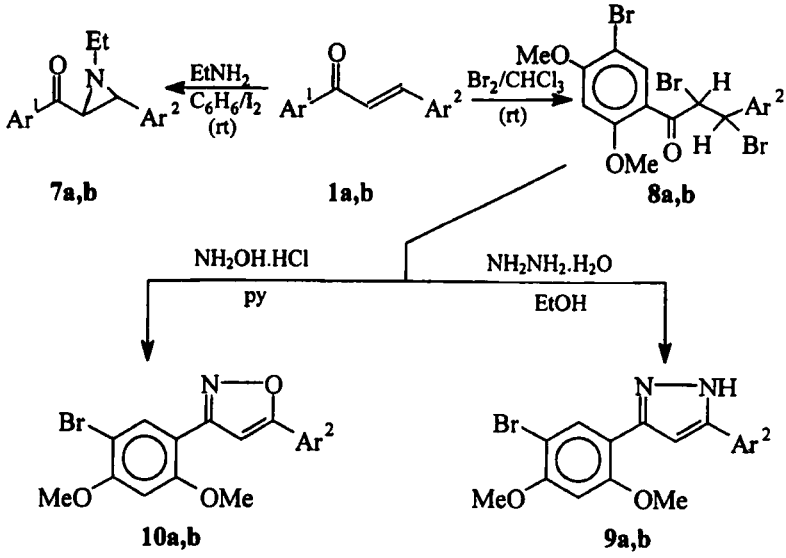
Hydrazine hydrate reacted with thiazines **2a,b** in refluxing ethanol to afford dihydropyrimidines **4a,b**, which are formed according to the mechanism in scheme 2.

Thioglycolic acid added readily to the alkenones **1a,b** in boiling acetic acid to afford the thioethers **5a,b** which displayed positive result when subjected to acidity test. Ammonium thiocyanate added, in presence of



SCHEME 2

sulfuric acid, to **1a** to furnish the adduct **6**. Aziridines could be synthesised via the reaction of a benzene solution of a primary amine with an α,β-unsaturated ketone at room temperature for several hours[8]. The addition of amine to an alkenone may be prompted by iodine. Thus when the chalcone **1a** or **1b** was allowed to react with ethylamine in benzene in the presence of iodine, it afforded the aziridine **7a** or **7b** (cf. Scheme 3).



SCHEME 3

TABLE I Physical Data of The New Compounds

Compd. No.	*Solvent of recrystall.*[a] *(Colour)*	*Yield (%)*	*MP (°C)*	*Mol.*[b] *Formula (M.wt.)*	
2a	B (yellow)	95	177–79	$C_{18}H_{17}ClN_2O_2S$	(360.5)
2b	B (yellow)	90	122–23	$C_{19}H_{18}N_2O_4S$	(370)
3a	B/L.P (yellow)	70	205–07	$C_{29}H_{25}Cl_2N_2O_5S$	(584)
3b	B/L.P (yellow)	71	190–92	$C_{28}H_{22}Cl_3N_2O_5S$	(604.5)
3c	B/L.P (reddish brown)	68	185–87	$C_{30}H_{27}ClN_2O_7S$	(594.5)
3d	Aq.E (yellow)	72	170–72	$C_{29}H_{24}Cl_2N_2O_7S$	(615)
4a	B/L.P (pale brown)	58	168	$C_{18}H_{18}ClN_4O_2$	(357.5)
4b	B/L.P (pale brown)	55	108–10	$C_{19}H_{19}N_4O_4$	(367)
5a	E (yellow)	82	153–54	$C_{19}H_{19}ClO_5S$	(394.5)
5b	M (yellow)	79	143–44	$C_{20}H_{20}O_7S$	(404)
6	M (pale brown)	63	80–82	$C_{18}H_{16}ClNO_3S$	(361.5)
7a	L.P (red)	55	126–27	$C_{19}H_{20}ClNO_3$	(345.5)
7b	L.P (brown)	57	117–18	$C_{20}H_{21}NO_5$	(355)
8a	L.P (pale red)	92	128–30	$C_{17}H_{14}ClO_3Br_3$	(544.5)
8b	L.P (pale red)	95	145–46	$C_{18}H_{15}O_5Br_3$	(554)
9a	M (yellow)	90	231–33	$C_{17}H_{14}ClN_2O_2Br$	(393.5)
9b	E (yellow)	88	167–69	$C_{18}H_{15}N_2O_2Br$	(404)
10a	M (white)	78	188–90	$C_{17}H_{13}ClNO_3Br$	(394.5)
10b	M (white)	75	190–91	$C_{18}H_{14}NO_5Br$	(405)

a. B = Benzene, L.P = Light petroleum, E = Ethanol, M = Methanol
b. Satisfactory microanalyses obtained C ± 0.48, H ± 0.29, N ± 0.37.

Bromination of the ethylenic ketones **1a,b** with excess bromine in chloroform by stirring at room temperature resulted in the formation of the tribromides **8a,b** which when allowed to react with hydrazine hydrate or hydroxylamine hydrochloride in refluxing ethanol and pyridine afforded the corresponding pyrazoles **9a,b** or isoxazoles **10a,b.**

TABLE II IR Spectra of Compounds **2–10**

Compd. No.	IR (KBr), ν (cm^{-1})
2a	1660 (C=N), 2960 (CH aliph), 3010 (CH arom), 3210 and 3260 (NH)
2b	1676 (C=N), 2972 (CH aliph), 3020 (CH arom), 3204 and 3385 (NH)
3a	1710-1720 (CO acid),
3b	1670-1680 (CO aroyl ketone),
3c	1640-1660 (C=N), 1590-1599 (C=C),
3d	3385, 3400 and 3427 (br NH)
4a	1611 (C=C), 1640(C=N), 2920 (CH aliph), 3080 (CH arom) and 3300 (br NH_2)
4b	1615 (C=C), 1650 (C=N), 2937 (CH aliph), 3095 (CH arom) and 3362 (br NH_2)
5a	1700 (CO acid), 1675 (CO aroyl), 1603 (C=C), 2922 (CH aliph), 3050 (CH arom) and 3435 (br OH)
5b	1710 (CO acid), 1680 (CO aroyl), 1610 (C=C), 2930 (CH aliph), 3088 (CH arom) and 3455 (br OH)
6	1660 (CO aroyl), 1610 (C=C) and 2100-2160 (very strong doublet SCN)
7a	1675 (CO aroyl), 1614 (C=C), 2926 (CH aliph), 3010 (CH arom)
7b	1678 (CO aroyl), 1618 (C=C), 2990 (CH aliph), 3072 (CH arom)
8a	1660 (CO aroyl), 1590 (C=C), 2910 (CH aliph) and 3000 (CH arom)
8b	1665 (CO aroyl), 1587 (C=C), 2930 (CH aliph) and 3020 (CH arom)
9a	1585 (C=C), 1695 (C=N), 2930 (CH aliph), 3110 (CH arom) and 3320 (br NH)
9b	1591 (C=C), 1618 (C=N), 2980 (CH aliph), 3057 (CH arom) and 3439 (br NH)
10a	1580 (C=C), 1610 (C=N), 2920 (CH aliph), and 3030 (CH arom)
10b	1590 (C=C), 1603 (C=N), 2987 (CH aliph), and 2987 (CH arom)

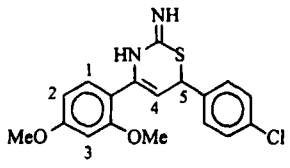
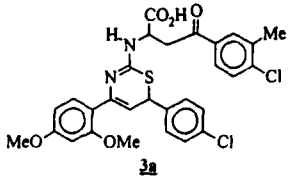
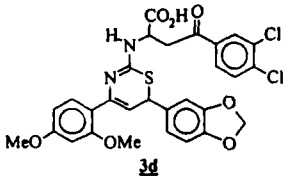
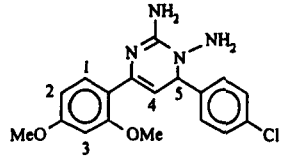
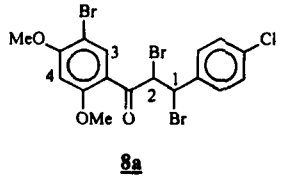
TABLE III Mass Spectroscopy of Compounds **4–10**

No.	*Compd. m/e (% of relative abundance)*
4a	358.8 $(M^{+\bullet}, 7.8)$, 326.5 (2.8), 315.5 (5.7), 248.8 (5.0), 222.5 (2.1), 207 (6.4), 184.5 (16.42), 179 (14.28), 167 (43), 165 (23), 163 (49.28), 151 (21), 138 (15), 137 (15), 111.5 (43.47), 97 (85.7), 77 (16.4) and *57 (100, base peak).*
5a	*395 (base and parent peak, 100),* 393 (78.6), 379 (1.0), 378 (2.9), 363 (1.4), 336 (1.0), 256 (6.4), 243 (96.4), 212 (12.9), 200 (23.6), 186 (17.1), 185 (20.2), 171.9 (28.6), 137 (10.7), 77 (15.4), 74.9 (45.7) and 60 (12.1).
6	360.9 $(M^{+\bullet}, 2.1)$, 362.9 (M+2, 0.85), 360.9 (7.1), 302.9 (1.4), 257.5 (3.1), 255.5 (5.0), 223 (1.8), 192 (7.9), *165 (100),* 137.9 (28.6), 137.5 (28.8), 121.8 (8.6), 106.9 (7.1), 77 (9.2), 75.8 (10.9) and 65 (1.0).
7a	345.8 ($M^{+\bullet}$, not observed), 332 $(M^{+\bullet} - Me^{\bullet} + H^{\bullet}, 8.1)$, 331 $(M^{+\bullet} - Me^{\bullet}, 5.9)$, 303 (17.8), 286 (43.7), 251 (9.6), *165 (100),* 138 (45.9), 122 (5.9) and 77 (6.7).
8a	542.5 $(M^{+\bullet}, 6.7)$, 462.5 (21.5), 382.5 (53.3), 354.1 (37), 340.1 (8.9), 301.2 (48.9), 270.2 (0.5), 255.1 (16.7), 245.1 (93.3), *243.1 (100),* 217.1 (2.2), 186.1 (8.1), 172 (17.0), 165 (37), 137 (19.1), 106 (4.4), 91 (22.2) and 75 (18.5).
9a	397.6 (M+4, 2.2)[a], 395.6 (M+2, 8.4), 393.6 $(M^{+\bullet}, 6.6)$, 314 (4.0), 176.1 (7.0), 153.1 (4.4), 99.3 (2.7), *82.0 (100)*[b], 80.0 (96.0).
10a	398.5 (M+4, 4.4)[a], 396.5 (M+2, 15.9), 394.5 $(M^{+\bullet}, 12.4)$, 243.0 (16.8), 197.6 (8.4), 169.0 (15.9), 111.2 (27.4), 85.1 (56.6), 82.0 (17.7), 71.0 (87.2) and *57.1 (100).*

a. The m/e values of M, M+2, M+4 fragments satisfy the fact that a compound having a combination of Br and Cl displays M+2 and M+4 fragments having 130% and 31.9% as intensities of isotope peaks relative to the molecular ion peak.

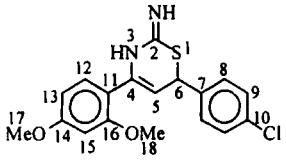
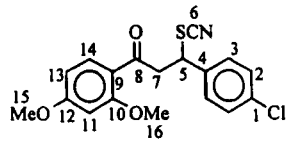
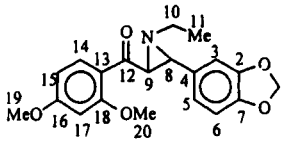
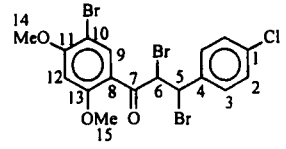
b. The base peak at m/e 82.0 is the isotope peak of the peak of m/e 80.0 which could be attributable to $\overset{+}{H}Br$

TABLE IV ^{1}H-NMR of Compounds **2, 3, 4** and **8**

Structural Formula and Compd. No.	*δ(ppm), Splitting, No. of H, J(Hz)*
 **2a**	3.20 and 3.30 (2s, 6H, 2 OMe), 4.95 (m, 1H, H-4), 5.10 (m, 1H, H-5), 6.30 and 6.40 (d × d, 2H, H-3 and H-2, $J_{1,2}$ = 6.00 and $J_{2,3}$ = 2.00), 6.9 (s, 1H, NH), 7.20–7.30 (m, 5H, H-1 and 4 arom H of -C_6H_4Cl-4) and 8.10 (s, 1H, =NH).
 **3a**	2.20 (s, 3H, Me), 3.40 and 3.45 (2s, 6H, 2 OMe), 4.15 (q, 2H, -CO-C<u>H</u>$_2$-CH-CO_2H), 4.90 (d, 1H, =CH-C<u>H</u>-S-), 6.20 (q, 1H, HN−C<u>H</u>−CH_2-), 8.10–8.40 (m, 11H, Ar- H), 9.0 (sbr, 1H, N<u>H</u>) and 10.6 (s, 1H, COO<u>H</u>).
 **3d**	3.40 and 3.45 (2s, 6H, 2 OMe), 4.10 (q, 2H, -CO-C<u>H</u>$_2$-CH-CO_2H), 4.90 (d, 1H, =CH-C<u>H</u>-S-), 5.70 (d, 2H, -O-C<u>H</u>$_2$-O), 6.20 (q, 1H, HN−C<u>H</u>−CH_2-), 8.25 (sbr, 1H, N<u>H</u>), 8.40–9.10 (m, 10H, Ar-H), and 10.7 (s, 1H, COO<u>H</u>).
 **4a**	1.17 and 2.20 (2s, 4H, 2 NH_2), 3.81 and 3.86 (2s, 6H, 2 OMe), 4.96 (m, 1H, H-4), 5.17 (m, 1H, H-5), 6.40 and 6.50 (dxd, H-3 and H-2, $J_{1,2}$ = 7.95, $J_{2,3}$ = 4.02).
 **8a**	3.75 and 3.83 (2s, 6H, 2 OMe), 5.32 and 5.37 (d, 1H, H-1, J = 11.5), 5.85 and 5.89 (d, 1H, H-2, J=11.5), 6.39 (s, 1H, H-4), 7.10–7.30 (m, 4H, C_6<u>H</u>$_4$Cl-4) and 7.9 (s, 1H, H-3). The ^{1}H-NMR of **8a** showed the presence of diastereomeric isomers in the ratio 1:12.

All compounds are dissolved in $CDCl_3$.

TABLE V ^{13}C-NMR of **2, 6, 7** and **8**

Structural Formula and Compd. No.	*δ(ppm)[a] Carbon atom's No.*
 **2a**	174.61 (C-2), 114.38 (C-4), 100.70 (C-5), 56.47 (C-6), 141.21 (C-7), 128.25 (C-8), 129.8 (C-9), 133.13 (C-10), 134.25 (C-11), 130.04 (C-12), 105.17 (C-13), 161.98 (C-14), 98.85 (C-15), 157.75 (C-16), 55.73 (C-17) and 55.41 (C-18).
 **6**	133.21 (C-1), 129.64 (C-2), 128.96 (C-3), 138.98 (C-4), 52.04 (C-5), 120.45 (C-6), 57.54 (C-7), 194.59 (C-8), 120.45 (C-9), 162 18 (C-10), 98.91 (C-11), 166.10(C-12), 106.91 (C-13), 130.57 (C-14), 55.48 (C-15) and 55.66 (C-16).
 **7b**	106.16 (C-1), 138.18 (C-2), 130.07 (C-3), 134.67 (C-4), 131.97 (C-5), 130.48 (C-6), 137.39 (C-7), 48.41 (C-8), 82.46 (C-9), 46.42 (C-10), 18.47 (C-11), 197.76 (C-12), 119.07 (C-13), 132.10 (C-14), 106.16 (C- 15), 164.64 (C-16), 98.43 (C-17), 161.19 (C-18), 55.87 (C-19), and 55.62 (C-20).
 **8a**	134.46 (C-1), 122.59 (C-2), 129.59 (C-3), 137.31 (C-4), 49.21 (C-5), 51.19 (C-6), 188.95 (C-7), 117.92 (C-8), 136.05 (C-9), 96.44 (C-10), 161.26 (C-11), 103.47 (C-12), 160.45 (C-13), 56.42 (C-14), and 56.32 (C- 15). The ^{13}C-NMR showed extra peaks which may be interpreted on the basis of the presence of diastereomerism of the tribromide **8a**.

a. All compounds are measured in $CDCl_3$ except **6** which was in DMSO-d_6.

BIOLOGICAL SCREENING OF SOME SELECTIVE SYNTHESISED COMPOUNDS

The antibacterial activities of some of the synthesised compounds were determined in vitro using the hole plate and filter paper disc method[9–11].

The tested compounds were dissolved in 10% acetone (v/v). The concentrations chosen were 25, 50 and 100 μg/mL and the results are summarized in table (VI).

TABLE VI Bacterial Activity (A*) and Minimum Inhibitory Concentration (MIC in μg/mL) of Some Newly Synthesiscd Compounds

Compd. No.	*Inhibition*			
	E.Coli		*S.Aureus*	
	A[a]	*MIC*	*A*[a]	*MIC*
2b	–	–	–	–
3b	+	100	+	100
3d	++	50	+	100
4b	–	–	–	–
5a	+++	25	++	50
8a	+++	25	+++	25
8b	+	100	+	100
9a	+	100	+	100
10a	–	–	+	100

a. The width of the zone of inhibition indicates the potency of antibacterial activity; (-) no antibacterial activity; (+) mild activity with the diameter of the zones eqaul to 0.6–0.8 cm, (++) moderate activity with the diameter of the zones eqaul to 1.2–1.3 cm;; (+++) marked activity with the diameter of the zones eqaul to 1.8–2.0 cm. *E.Coli* is a Gram- negative and *S.Aureus* is a Gram-positive bacteria.

CONCLUSION

From Table (VI), the results show that compounds **5a, 8a** and **8b** were the most effective against both Gram-negative and Gram-positive bacterial strains whereas some other compounds have moderate effect on the tested bacteria. We can conclude that compounds **5a, 8a** and **8b** can be used as antibacterial agents against both Gram-negative and Gram-positive bacteria.

EXPERIMENTAL

Melting points are uncorrected. 1R spectra were recorded using KBr wafer technique[12]. ^{1}H- and ^{13}C-NMR spectra were determined on

AC.250(20MHz) Bruker[13,14]. In all NMR measurements, the internal standard was TMS and all chemical shifts are in ppm downfield from TMS. The mass spectra were determined using MS-TSQ 70 Finnigan MAT and GCMS-QP1000 EX Shimadzu, Japan, EI = 70 ev.

Reaction of thiourea with 1,3-diarylprop-2-enones 1a,b; formation of 2-amino-4,6-diarylthiazines 2a,b

A mixture of **1a** or **1b** (0.01 mol), thiourea (0.015 mol, 1.14 g) and alcoholic sodium ethoxide (0.23 g of sodium metal) in 30 mL absolute ethanol was heated under reflux with stirring for 4 h, cooled and poured into dil. HCl/ice. The solid products that separated out were filtered off, washed with cold water, dried and then recrystallized from suitable solvent to yield the thiazine derivatives **2a** or **2b** (cf. Table I).

Reaction of thiazine derivatives 2a,b with β-aroylacrylic acids; formation of 2-[4,6-diaryl-1,3-thiazin-2-yl]amino-4-aryl-4-oxo-butanoic acids 3a-d

A solution of thiazine derivative **2a** or **2b** (0.01 mol), 2-(3-methyl-4-chlorobenzoyl)acrylic acid or 2-(3,4-dichlorobenzoyl)acrylic acid (0.01 mol) in dry benzene (30 mL) was stirred for 20 minutes at room temperature then a few drops of piperidine (1.0 mL) were added dropwise with continued stirring. The reaction mixture was then heated under reflux with stirring for 8 h and then left to cool. Most of the organic solvent was removed using a rotary evaporator to afford a semisolid which was triturated with light petroleum 60–80°C to yield the crude solid product which was recrystallized from the proper solvent to give **3a-d**.

Reaction of thiazine derivatives 2a,b with hydrazine hydrate; formation of 1,2-diamino-6-aryl-4-(2,4-dimethoxyphenyl)1, 2-dihydropyrimidines 4a,b

To a solution of thiazine derivative **2a** or **2b** (0.01 mol) in 30 mL ethanol, hydrazine hydrate (80%), 0.015 mol, 0.75 mL, was added and the solution was refluxed for 6 h, cooled and poured into ice/water. The solid which

precipitated was filtered off, washed with water, dried and finally recrystallised from the suitable solvent to yield the dihydropyrimidines **4a** or **4b**.

Reaction of 1a,b with thioglycolic acid; formation of 3-aryl-3-carboxy-methylthio-1-(2,4-dimethoxyphenyl)propanones 5a,b

A mixture of 1,3-diarylprop-2-en-1-one **1a** (0.01 mol) or **1b** and thioglycolic acid (0.012 mol, 1.3 g) in 20 mL glacial acetic acid was refluxed with stirring for 3 h. The reaction mixture was left to cool then poured into ice/water. The crude solid was filtered by suction, washed with cold water, dried and finally recrystallized from the suitable solvent to give **5a**or **5b**.

Reaction of 1a with ammonium thiocyanate; formation of 3-(4-chlorophenyl)-1-(2,4-dimethoxyphenyl)-3-thiocyanato-propanone 6

To a solution of **1a** (0.01 mol, 3.02 g) in 10 mL sulfuric acid (20%) was added an aqueous solution of ammonium thiocyanate (0.05 mol, 4.0 g) in 10 ml of water. The reaction mixture was stirred for 3 hrs at room temperature. The organic product was extracted with diethyl ether and dried over anhydrous magnesium sulfate. Evaporating ether resulted in a solid product which was recrystallised to afford **6**.

Reaction of 1a or 1b with ethylamine; formation of 2-aryl-3-(2,4-dimethoxybenzoyl)-N-ethylaziridines 7a,b

A solution of iodine (0.025 mol, 6.35 g) in 50 mL dry benzene was added over a period of 25 minutes to a mixture of **1a** or **1b** (0.025 mol) and ethylamine (0.01 mol, 5 mL) in 75 mL of dry benzene. The colour of iodine solution was discharged as rapidly as it was added until 35 mL had been introduced. After the addition was complete, the solution was reddish brown in colour but after continuing stirring for an additional hour, the color changed to a light yellow-orange. The precipitated hydroiodide was removed by filtration and the organic solution was washed with water several times and dried over anhydrous $MgSO_4$.

Evaporation of the solvent using a rotary evaporator resulted in a solid which was recrystallized from the proper solvent to give the aziridine derivatives **7a** or **7b**.

Reaction of 1a or b with bromine; formation of 2,3-dibromo-1-(5-bromo-2,4-dimethoxyphenyl)-3-(4-chlorophenyl)/-(3,4-methylenedioxyphenyl)- propanones 8a,b

A solution of bromine (0.03 mol, 1.5 mL) in chloroform (2 mL) was added dropwise, with continuous stirring at room temperature, to a solution of **1a** or **1b** in chloroform (20 mL) within 30 minutes. Most of the solvent was removed using a rotary evaporator to afford a semisolid which was washed with water several times then triturated with light petroleum 40–60°C to give crude solid product which was recrystallized from the suitable solvent to yield the tribromides **8a** or **8b**.

Reaction of 8a or 8b with hydrazine hydrate; formation of 5-aryl-3-(5-bromo-2,4-dimethoxyphenyl)pyrazoles 9a or 9b

To a solution of **8a** or **8b** (0.01 mol) in ethanol (20 mL), 80% hydrazine hydrate (0.015 mol, 0.75 ml) was added and the reaction mixture was refluxed for 4 h, cooled and diluted with water. The solid products that separated out were collected by filtration, dried then recrystallized from the proper solvent to give **9a** or **9b**.

Reaction of 8a or 8b with hydroxylamine hydrochloride; formation of 5-aryl-3-(5-bromo-2,4-dimethoxyphenyl)isoxozoles 10a or 10b

To a solution of **8a** or **8b** (0.01 mol) in dry pyridine (10 mL), hydroxylamine hydrochloride (0.015 mol, 1.55 g) in dry pyridine (20 mL) was added dropwise with stirring at room temperature for 20 minutes. The reaction mixture was heated under reflux for 6 h, cooled and poured into HCl/ice. The solid products that precipitated were filtered off, washed with cold water several times, dried and then recrystallized from the suitable solvent to yield the isoxazoles **10a** or **10b**.

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