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Synthesis of new 4-aryl-isoxazolo[5,4-*d*]pyrimidin-6-one(thione) and 4-aryl-pyrazolo[3,4-*d*]-pyrimidin-6-one derivatives of potential antihypertensive activity

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Some aromatic aldehydes are subjected to react with urea (or thiourea) and acetyl acetone in a one-pot Biginelli-type cyclocondensation reaction to give 5-acetyl-4-aryl-6-methyl-1,2,3,4-tetrahydro-pyrimidines **2a-j**. Aldehydes with *ortho*-hydroxy substituent namely salicylaldehyde and 2-hydroxy-3-methoxybenzaldehyde undergo Michael-type addition of the hydroxyl-proton to the C_5–C_6 double bond of the pyrimidine ring to form the tricyclic derivatives **3a-d** while 2-hydroxy-3-nitrobenzaldehyde reacted normally to give **2j**. Compounds from the type **2** react with basic hydroxylamine to give the respective isoxazolopyrimidine derivatives **4a-g** through an intramolecular addition of the oxim-hydroxyl proton to the C_5–C_6 double bond of the pyrimidine ring. The oxime derivatives from the tricyclic compounds **3a,c** undergo rupture of the oxacyclic ring followed by addition of the oxim-proton to the C_5–C_6 double bond of the pyrimidine ring giving rise to the corresponding isoxazolophenols **5a**,**b**. Furthermore, when hydrazine hydrate reacts with the acetyl derivatives **2a**, **2f** and 2h afford the corresponding 4-aryl-5-(1-hydrazono-ethyl)-6-methyl-3,4-dihydro-1*H*-pyrimidin-2-one **6a-c**, while the compounds **2d** and **3c** react under the same reaction conditions to give the pyrazolopyrimidine derivatives **7** and **8**, respectively.

Keywords: Biginelli reaction, 1,2,3,4-tetrahydropyrimidines, pyrimidin-6-one, antihypertensive activity

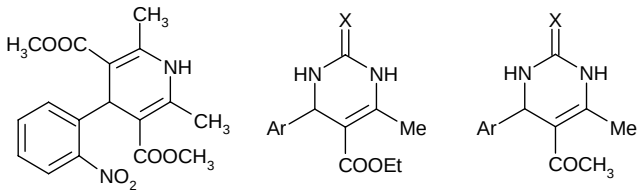
IPC Code: Int.Cl.[8] C07D

In recent years, 4-aryl-6-methyl-2-oxo-(thio)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester **1** known as the Biginelli compounds[1] have received significant attention owing to their structural relationship with the clinically active dihydropyridine calcium channel blockers (nifedipines). In addition, they have been reported to possess diverse range of biological properties as e.g. antitumor[2-4], analgesic[5], anti-inflammatory[6], antibacterial and antiviral[7-10]. Some of these compounds are very potent calcium channel blockers and are used for treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias or angina[11-18]. Moreover, the presence of different interacted functional groups determines their great synthetic potential[3,19-22].

Whereas the standard Biginelli compounds have been of synthetic interest during the last two decades, little attention has been focused on the structurally similar 5-acetyl derivatives **2** (ref.23).

In this investigation, we found an interesting approach to synthesize isoxazole- and pyrazole-ring systems fused with the pyrimidine nucleus through the 5-acetyl group.

Preparation of 5-acetyl-4-aryl-6-methyl-2-oxo-(thio)-1,2,3,4-tetrahydropyrimidine **2** is practically similar to that reported by Biginelli[1], except the type of the catalyst used, i.e., by the one-pot-reaction between an aldehyde, urea (thiourea) and acetylacetone in ethanol acidified with few drops of acetic acid.



Nifedipine **1** X = O, S **2**

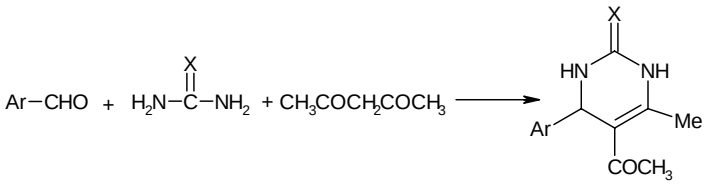
Thus, benzaldehyde, 2-nitrobenzaldehyde, 3,4-dimethoxybenzaldehyde, 3,4,5-trimethoxy-benzaldehyde, 4-hydroxy-3-methoxybenzaldehyde and 2-hydroxy-3-nitrobenzaldehyde reacted with urea (or thiourea) and acetylacetone in ethanol acidified with few drops of acetic acid to give the corresponding 5-acetyl-4-aryl-6-methyl-2-oxo(thio)-1,2,3,4-tetrahydro-pyrimidines **2a-j**, respectively (**Scheme I**).

Aldehydes with a hydroxyl group in the *ortho* position gave products differ according to their structures. Thus, while 2-hydroxy-3-nitrobenzaldehyde reacted normally and gave **2j**, salicylaldehyde and 2-hydroxy-3-methoxybenzaldehyde on the other hand, afforded the corresponding 6-substituted 13-acetyl-9-methyl-8-oxa-10,12-diaza-tricyclo-[7.3.1.0*2,7*]trideca-2,4,6-trien-11-one (thione), **3a-d**, resulted by addition of the phenolic proton to the C_5–C_6 double bond of the pyrimidine ring (**Scheme II**). This Michael-type intramolecular interaction was reported previously with the standard Biginelli compounds[24].

^{1}H NMR spectra of the compounds **3a-d** showed the presence of signals around δ 3.3 ppm correspond to the –C_5 protons and appeared as doublets, this is in addition to the protons at –C_4 which appeared as triplets in the range of δ 4.8-5.4 (see experimental). Also, the signals corresponding to the methyl group at –C_6 shifted to a higher magnetic field (δ, 1.5-1.6) when compared with those of compounds **2**, indicating its attachment to a quaternary carbon not to a double bond.

Reaction of the acetyl derivatives **2a-f**, **h** with basic hydroxyl amine afforded 4-aryl-3,7a-dimethyl-4,5,7,7a-tetrahydro-3a*H*-isoxazolo[5,4-*d*]pyrimidin-6-ones(thiones) **4a-g** formed by intramolecular interaction between the oxim-hydroxyl proton and the C_5–C_6 double bond of the pyrimidine ring in a fashion similar to the phenols described above (**Scheme III**).

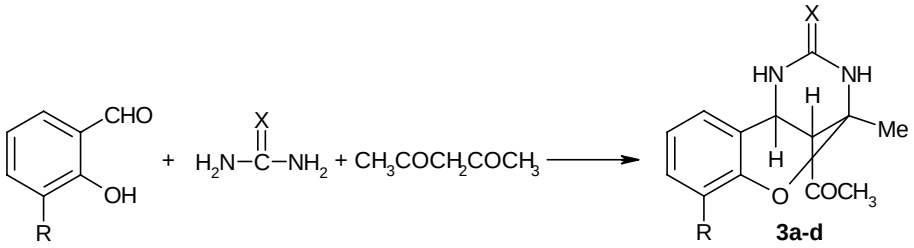
As was found with the tricyclic compounds **3**, the ^{1}H NMR spectra of compounds **4a-g** showed the presence of signals aroundδ 3.3, correspond to the –C_5 protons and appeared as doublets, this is in



2a-j

2a, Ar = phenyl, X = O, **2b**, Ar = phenyl, X = S, **2c**, Ar = 2-nitrophenyl, X = O
2d, Ar = 3,4-dimethoxyphenyl, X = O, **2e**, Ar = 3,4-dimethoxyphenyl, X = S
2f, Ar = 3,4,5-trimethoxyphenyl, X = O, **2g**, Ar = 3,4,5-trimethoxyphenyl, X = S,
2h, Ar = 4-hydroxy-3-methoxyphenyl, X = O, **2i**, Ar = 4-hydroxy-3-methoxyphenyl, X = S
2j, Ar = 2-hydroxy-3-nitrophenyl, X = O

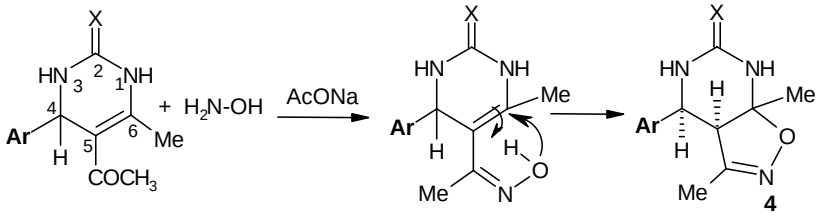
Scheme I



3a-d

3a, R = H, X = O, **3b**, R = H, X = S
3c, R = OMe, X = O **3d**, R = OMe, X = S

Scheme II



4

4a, Ar = phenyl, X=O. **4b**, Ar = phenyl, X=S. **4c**, Ar = 2-nitrophenyl, X=O
4d, Ar = 3,4-dimethoxyphenyl, X=O. **4e**, Ar = 3,4-dimethoxyphenyl, X=S
4f, Ar = 3,4,5-trimethoxyphenyl, X=O. **4g**, Ar = 4-hydroxy-3-methoxyphenyl, X=O

Scheme III

addition to the protons at $-C_4$ which appeared as triplet around δ 4.5 (see experimental). Also, remarkable shifts to higher magnetic field for the signals correspond to the methyl group (around δ 1.0). In addition, their IR spectra lack the peaks due to the hydroxyl group.

Furthermore, reaction of the compounds **3a** and **3c** with hydroxyl amine caused rupture of the oxacyclic ring with formation of the corresponding isoxazole derivatives **5a** and **5b** (**Scheme IV**).

The structures of the products **5** were confirmed by the remarkable shift of the signal correspond to the methyl group at $-C_6$ in their ^{1}H NMR spectra to higher magnetic field due to the change from 6- to 5-membered ring and the appearance of the signal due to OH group in their IR spectra.

The reaction of hydrazine hydrate with the acetyl derivatives, **2a, 2d, 2f, 2h** and **3c** was also studied.

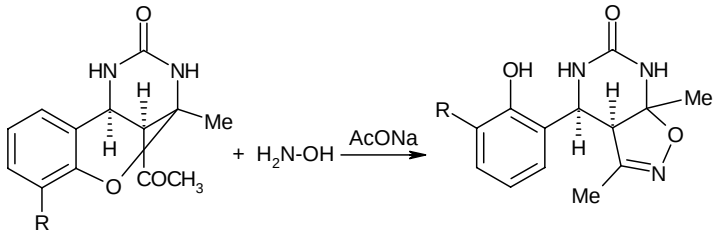
Thus, hydrazine hydrate and each of 5-acetyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetra-hydropyrimidine **2a**, 5-acetyl-6-methyl-2-oxo-4-(3′,4′,5′-trimethoxy-phenyl)-1,2,3,4-tetrahydropyrimidine **2f** and 5-acetyl-4-(4-hydroxy-3-methoxyphenyl)-6-methyl-2-oxo-1,2, 3,4-tetrahydropyrimidine **2h**, furnished the corresponding 5-(1-hydrazonoethyl)-6-methyl-4-phenyl-3,4-di-hydro-1*H*-pyrimidin-2-one **6a**, 5-(1-hydrazonoethyl)-6-methyl-4 - (3′,4′,5′-trimethoxyphe-nyl-3,4-dihydro-1*H*-pyrimidin-2-one **6b** and 5-(1-hydrazonoethyl)-4-(4′-hydroxy-3′-methoxyphenyl)-6-methyl-3,4-dihydro-1*H*-pyrimidin-2-one **6c**, respectively.

On the other hand, 5-acetyl-4-(3′,4′-dimethoxy-phenyl)-6-methyl-2-oxo - 1,2,3,4-tetrahydropyrimidine **2d** afforded 4-(3′,4′-dimethoxyphenyl)-3,7a-dimethyl-1,3a,4,5,7,7a-hexahydro-pyrazolo[3,4 - *d*]pyrimidin-6-one **7**. Also, 13-acetyl-6-methoxy-9-methyl-8-oxa-10,12-diazatri - cyclo[7.3.1.0*2,7*]trideca-2,4,6-trien-11-one **3c** reacted with rupture of the oxa-cyclic ring to furnish the corresponding 4-(2′-hydroxy-3′-methoxyphenyl) - 3,7a-dimethyl-1,3a,4,5,7,7a-hexahy-dropyrazolo-[3,4-*d*]pyrimidin-6-one **8** (**Scheme V**).

As was found with the isoxazole compounds **4,** the ^{1}H NMR spectra of **7** and **8** revealed the appearance of signal due to proton at $-C_5$, in addition to the signal corresponds to the methyl group which has shifted to higher magnetic field (see experimental).

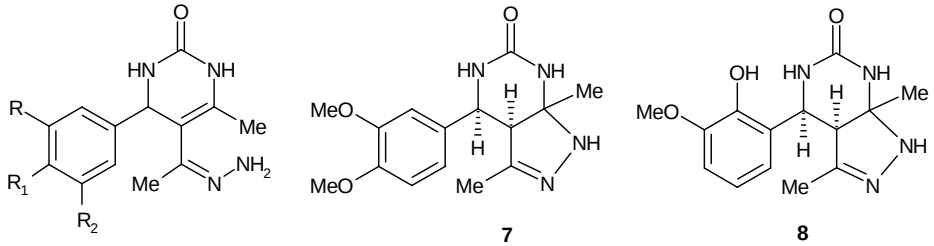
Antihypertensive activity

Antihypertensive activity of six of the studied compounds **3c**, **4g**, **5a**, **5b**, **7** and **8**, (**Table I**) was measured using seventy eight male Sprague Dawly rats (230-250 g). The rats were acclimatized for 1 week in the animal facility that has 12 hr light/dark cycles with the temperature controlled at 21° to 23°C. The rats were injected with 10 mg/kg deoxycorticosterone acetate (DOCA) subcutaneously and the animals fed high diet (8% NaCl) for 3-4 weeks. Their blood pressure (BP) was recorded 24 hr before starting the treatment with different synthetic drugs. Blood pressure was measured using the tail-cuff method in conscious rats[25].



3a, R=H; **3c**, R=OMe **5a**, R=H **5b**, R=OMe

Scheme IV



6a, R = R_1 = R_2 = H
6b, R = R_1= R_2 =OMe
6c, R = OMe, R_1 = OH, R_2 = H

7 **8**

Scheme V

Statistical analysis and the results of the tests are given in **Table I**.

Results and Discussion

It appears from the table that, the decrease in the blood pressure obtained by using compound **3c** is higher than that obtained by nifedipine (control), while that of **5b** is close to the value of obtained by nifedipine. The values obtained by the compounds **7, 8** and **4g** are comparable and are still close to the control sample. Compound **5a** is considered to be inactive. These preliminary results are encouraging and promising. The variation in the activity may be tentatively explained by the variation in the structure of the aromatic ring. This result is however in accord with many of Biginelli compounds of similar aromatic substituents, in which the anti-hypertensive activity is largely dependent on the substitution on the aromatic nucleus. The lack of the activity found with compound **5a** can be explained by the presence of free OH group in the *ortho*-position of the aromatic ring which may play some roll in the activity. The presence of a neighboring group (compounds **5b** and **8**) that can interact with the hydroxyl group (e.g. conjugation) will prevent this effect to take place. A pharmacological study for all the compounds of this investigation will be reported separately.

Table I — The mean arterial blood pressure of hypertensive rats post-treated (after 2hr) with single oral doses of nifedipine and tested compounds (5 mg /Kg b wt)

Groups	Hg, mm
Normal control	104.00 ±1.18
Hypertensive control	132.17 ± 2.20
Nifedipine	109.0 ± 1.90
3c	107.8 ± 1.50
5b	111.8 ± 1.60
7	112.5 ± 1.04
8	113.8 ± 1.50
4g	114.0 ± 1.20
5a	124.0 ± 1.35

Experimental Section

Melting points were taken on a capillary melting point apparatus and are uncorrected. The IR spectra were recorded with a Philips Infracord Spectrometer Model PU9712 in KBr discs. ^{1}H NMR spectra were measured in $CDCl_3$ and DMSO-d_6 on a JEOL-270 spectrometer with TMS as an internal standard. Mass spectra were obtained with a Schimadzu GCS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were performed at the Microanalytical Laboratory of the National Research Centre. The results of elemental analysis, melting points and yields are given in **Table II** and the physical data in **Table III**.

General procedure for preparation of 5-acetyl-4-aryl-6-methyl-2-oxo-(thio)-1,2,3,4-tetra-hydropyrimidine 2a-j and 6-substituted 13-acetyl-9-methyl-8-oxa-10,12-diaza-tricyclo-[7.3.1.0*2,7*]-trideca-2, 4,6-trien-11-one(thione) 3a-d. The aldehyde compound (10 mmoles), urea or thiourea, (22 mmoles), and acetyl acetone (1.4 g, 14 mmoles) in ethanol (50 mL) acidified with acetic acid (1 mL) were heated under reflux until completion of the reaction (4-8 hr, monitored by TLC). The reaction mixture was evaporated under vacuum and the product was treated with water and the solid formed was filtered. It was washed with water, dried and crystallized.

Table II — Characterization data of the prepared compounds

Compd	Yield (%)	M.p. °C (solvent)	Mole. formula (Mol. wt)	Calcd. % (Found)			
				C	H	N	S
2a	87	234-37 (EtOH)	$C_{13}H_{14}N_2O_2$ (230.27)	67.81 (67.75	6.13 6.20	12.17 12.10	- -)
2b	75	210-13 (EtOH)	$C_{13}H_{14}N_2OS$ (246.33)	63.39 (63.25	5.73 5.80	11.37 11.30	13.02 12.85)
2c	69	212-14 (Methanol)	$C_{13}H_{13}N_3O_4$ (275.27)	56.73 (56.65	4.76 4.70	15.27 15.10	- -)
2d	82	205-07 (EtOH)	$C_{15}H_{18}N_2O_4$ (290.32)	62.06 (61.80	6.25 6.30	9.65 9.50	- -)
2e	85	294-97 (EtOH/H_2O)	$C_{15}H_{18}N_2O_3S$ (306.39)	58.80 (58.70	5.92 6.10	9.14 9.10	10.47 10.30)
2f	69	203-05 (EtOH/H_2O)	$C_{16}H_{20}N_2O_5$ (320.35)	59.99 (60.10	6.29 6.10	8.74 8.65	- -)
2g	77	185-88 (EtOH)	$C_{16}H_{20}N_2O_4S$ (336.41)	57.13 (57.00	5.99 6.20	8.33 8.10	9.53 9.30)

Contd —

Table II — Characterization data of the prepared compounds — *Contd*

Compd	Yield (%)	M.p. °C (solvent)	Mole. formula (Mol. wt)	Calcd % (Found)			
				C	H	N	S
2h	80	230-234 (MeOH)	$C_{14}H_{16}N_2O_4$ (276.29)	60.86 (60.80	5.84 5.95	10.14 10.00	- -)
2i	90	210-14 (dil. Acetone)	$C_{14}H_{16}N_2O_3S$ (292.36)	57.52 (57.25	5.52 5.80	9.58 9.40	10.97 11.10)
2j	62	181-85 ($EtOH/H_2O$)	$C_{13}H_{13}N_3O_5$ (291.27)	53.61 (53.50	4.50 4.60	14.43 14.40	- -)
3a	69	215-18 (EtOH)	$C_{13}H_{14}N_2O_3$ (246.27)	63.40 (63.30	5.73 5.60	11.38 11.38	- -)
3b	69	257-61 ($Dioxane/H_2O$)	$C_{13}H_{14}N_2O_2S$ (262.33)	59.52 (59.35	5.38 5.50	10.68 10.60	12.22 12.10)
3c	58	245-47 (EtOH)	$C_{14}H_{16}N_2O_4$ (276.29)	60.86 (60.80	5.84 5.90	10.14 10.00	- -)
3d	72	240-43 (EtOH)	$C_{14}H_{16}N_2O_3S$ (292.36)	57.52 (57.45	5.52 5.60	9.58 9.50	10.97 10.80)
4a	75	226-29 ($EtOH/H_2O$)	$C_{13}H_{15}N_3O_2$ (245.28)	63.66 (63.60	6.16 6.30	17.13 17.05	- -)
4b	75	181-84 (EtOH)	$C_{13}H_{15}N_3OS$ (261.35)	59.75 (59.65	5.79 5.80	16.08 15.80	12.27 12.20)
4c	72	156-58 (EtOH)	$C_{13}H_{14}N_4O_4$ (290.28)	53.79 (53.70	4.86 5.00	19.30 19.10	- -)
4d	65	259-62 ($MeOH/H_2O$)	$C_{15}H_{19}N_3O_4$ (305.34)	59.01 (59.00	6.27 6.40	13.76 13.65	- -)
4e	92	246-48 (EtOH)	$C_{16}H_{21}N_3O_5$ (335.36)	57.30 (57.40	6.31 6.40	12.53 12.50	- -)
4f	89	248-50 (EtOH)	$C_{14}H_{17}N_3O_4$ (291.31)	57.72 (57.60	5.88 6.00	14.42 14.30	- -)
4g	84	230-234 (EtOH)	$C_{14}H_{17}N_3O_3S$ (307.37)	54.71 (54.45	5.57 5.70	13.67 13.55	10.43 10.30)
5a	73	295-297 ($EtOH/H_2O$)	$C_{13}H_{15}N_3O_3$ (261.28)	59.76 (59.70	5.79 5.80	16.08 15.80	- -)
5b	88	290-95 ($Acet./H_2O$)	$C_{14}H_{17}N_3O_4$ (291.31)	57.72 (57.55	5.88 6.00	14.42 14.20)	
6a	69	220-24 (EtOH)	$C_{13}H_{16}N_4O$ (244.31)	63.92 (63.65	6.60 6.80	22.93 22.70)	
6b	82	220-24 (MeOH)	$C_{16}H_{22}N_4O_4$ (334.38)	57.47 (57.20	6.63 6.90	16.76 16.70)	
6c	71	190-193 (EtOH)	$C_{14}H_{18}N_4O_3$ (290.32)	57.92 (57.80	6.25 6.30	19.30 18.90)	
7	70	212-14 (Ethanol)	$C_{15}H_{20}N_4O_3$ (304.35)	59.20 (59.10	6.62 6.70	18.41 18.30)	
8	63	175-78 (Ethanol)	$C_{14}H_{18}N_4O_3$ (290.32)	57.92 (57.75	6.25 6.40	19.30 19.20)	

Table III — ^{1}H NMR and mass spectra of the prepared compounds

Compd	Mass spectra MS, m/z, (%)	^{1}H NMR, δ, ppm
2a	230.27 (78%, M^+), 229, (91, M^+-1), 215 (49, M^+-CH_3), 187 (39, M^+-$COCH_3$), & 153 (100, pyrimidine moiety)	(DMSO-d_6): 9.10 (s, 1H, N_1H), 7.45 (t, 2H, ArH-C_4'&C_5'), 7.3 (m, 3H, ArH-C_2', C_3' & C_6'), 6.5 (d, 1H, N_3H), 5.6 (d, 1H, C_4H), 2.32 (s, 3H, $COCH_3$), and 2.13 (s, 3H, CH_3).
2b	246.2 (100, M^+), 203 (49, M^+-$COCH_3$), 169 (82, pyrimidine moiety)	(DMSO-d_6): 8.17 (s, 1H, N_1H), 7.6 (d, 1H, N_3H), 6.51 (d & t, 5H, ArH), 5.5 (d, 1H, C_4H), 2.30 (s, 3H, $COCH_3$) & 2.10 (s, 3H, CH_3).
2c	276 (2, M^++1), 258 (9, M^+-OH), 215 (49, M^+-OH -$COCH_3$), 198 (100)	(DMSO-d_6): 9.37 (s, 1H, N_1H), 7.9 (d, 1H, N_3H), 7.67 (m, 2H, ArH), 7.48 (m, 2H, ArH), 5.9 (d, 1H, C_4H), 2.36 (s, 3H, $COCH_3$) & 2.13 (s, 3H, CH_3).

Contd

Table III — ^{1}H NMR and mass spectra of the prepared compounds — *Contd*

Compd	Mass spectra MS, m/z, (%)	^{1}H NMR, δ, ppm
2d	290.2 (100, M^+), 275 (83, M^+- Me), 259 (55, M^+-OH-CH_3 + H), 247 (48, (M^+-$COCH_3$) & 153 (79)	($CDCl_3$): 7.70 (s, 1H, N_1H), 6.85 and 6.78 (m, 3H, ArH), 5.82 (s, 1H, N_3H), 5.41 (s, 1H, C_4H), 3.85 (s, 6H, 2 OCH_3), 2.36 (s, 3H, $COCH_3$), & 2.12 (s, 3H, CH_3).
2e	306 (100, M^+), 263 (M^+-$COCH_3$), & 169 (45)	($CDCl_3$), 7.70 (s, 1H, N_1-H), 7.31 (s, 1H, N_3H), 6.81 (s, 2H, ArH), 6.78 (s, 1H, ArH), 5.40 (d, 1H, C_4H), 3.86 (s, 6H, 2 OCH_3), 2.35 (s, 3H, $COCH_3$), and 2.14 (s, 3H, CH_3).
2f	320.1 (100, M^+), 305.1 (56, M^+-CH_3), 289 (70, M^+-OMe), 277 (22.5, M^+-Ac) & 153 (43)	(DMSO-d_6): 9.10 (s, 1H, N_1H), 7.70 (s, 1H, N_3H), 6.58 (s, 2H, ArH), 5.22 (d, 1H, C_4H), 3.75 (s, 6H, 2 OCH_3), 3.62 (s, 3H, OCH_3), 2.35 (s, 3H, $COCH_3$), and 2.15 (s, 3H, CH_3).
2g	336.1 (100, M^+), 305.1 (28, M^+-OCH_3), 293 (16, M^+-Ac), 169 (18, pyrimidine moiety)	(DMSO-d_6): 8.50 (s, 1H, N_1H), 7.60 (s, 1H, N_3H), 6.60 (s, 2H, ArH), 5.20 (d, 1H, C_4H), 3.75 (s, 6H, 2 OCH_3), 3.65 (s, 3H, OCH_3), 2.35 (s, 3H, $COCH_3$), and 2.15 (s, 3H, CH_3).
2h	276 (100, M^+), 233 (30, M^+-Ac) & 153 (49)	(DMSO-d_6): 9.10 (s, 1H, N_1H), 8.84 (s, 1H, OH), 7.62 (s, 1H, N_3H), 6.82 (d, 1H, $ArC_2'H$), 6.70 (d, 1H, $C_5'H$), 6.6 (dd, 1H, $C_6'H$), 5.18 (d, 1H, C_4H), 3.75 (s, 3H, OCH_3), 2.25 (s, 3H, $COCH_3$), 2.15 (s, 3H, CH_3).
2i	292 (100, M^+), 249 (56, M^+-$COCH_3$) & 169 (25)	(DMSO-d_6): 9.00 (s, 1H, OH), 8.15 (s, 1H, N_1H), 7.45 (s, 1H, N_3H), 6.78 (d, 1H, C2′-H), 6.70 (d, 1H, C5′H), 6.56 (dd, 1H, $C_6'H$), 5.20 (d, 1H, C_4H), 3.78 (s, 3H, OCH_3), 2.25 (s, 3H, $COCH_3$), 2.10 (s, 3H, CH_3).
2j	291 (12, M^+), 274 (100, M^+-OH), 248 (40.5, M^+-$COCH_3$)	(DMSO-d_6): 11.46 (s, 1H, OH), 9.24 (s, 1H, N_1H), 8.06 (d, 1H, Ar-$C_4'H$), 7.84 (d, 1H, C6′-H), 7.50 (s, 1H, N^3-H), 7.01 (t, 1H, $C_5'H$), 5.55 (d, 1H, C_4H), 2.24 (s, 3H, $COCH_3$) and 2.07 (s, 3H, CH_3)
3a	246 (20, M^+), 229 (33, M^+-OH), 203 (88, M^+- $COCH_3$) & 189 (100, M^+- CH_2-Ac)	(DMSO-d_6): 7.41 (s, 1H, N_1H), 7.60 (m, 2H, ArH), 7.05 (d, 1H, N_3H), 6.90 (t, 1H, ArH), 6.77 (d, 1H, ArH), 4.63 (t, 1H, C_4H), 3.36 (d, 1H, C5-H), 2.28 (s, 3H, $COCH_3$), and 1.56 (s, 3H, CH_3)
3b	262 (95), 259 (100) & 249 (92, M^+- Ac)	(DMSO-d_6): 8.05 (s, 1H, N^1-H), 7.45 (s, 1H, N_3-H), 6.90 (t, 1H, ArH), 6.77 (d, 1H, ArH), 6.70 (m, 2H, ArH), 4.60 (t, 1H, C_4H), 3.32 (s, 1H, C_5H), 2.28 (s, 3H, $COCH_3$), and at 1.56 (s, 3H, CH_3).
3c	276, 95%, the base peak ion at m/z 259, and 233, 92% (M^+- $COCH_3$).	(DMSO-d_6): 7.37 (s, 1H, N_1H), 7.02 (d, 1H, N_3H), 6.80 (m, 3H, ArH), 4.60 (t, 1H, C_4H), 3.70 (s, 3H, OCH_3), 3.33 (s, 1H, C_5H), 2.28 (s, 3H, $COCH_3$), and 1.66 (s, 3H, CH_3).
3d	292.2 (100, M^+)	(DMSO-d_6): 8.37 (s, 1H, N_1H), 7.60 (d, 1H, N_3H), 6.65 (m, 3H, ArH), 4.60 (t, 1H, C_4H), 3.76 (s, 3H, OCH_3), 3.32 (s, 1H, C_5H), 2.28 (s, 3H, $COCH_3$), and 1.55 (s, 3H, CH_3).
4a	246 (5.8, M^++1), 77 (100, C_6H_5)	(DMSO-d_6): 7.40-7.23 (m, 6H, 5 ArH + 1N_3H), 7.05 (s, 1H, N_1H), 4.69 (s, 1H, C_4H), 3.72 (s, 1H, C_5H), 1.97 (s, 3H, $COCH_3$), and at 1.02 (s, 3H, CH_3).
4b	261.1 (78, M^+), 244 (100, M^+-OH)	(DMSO-d_6): 8.9 (s, 1H, N^3H); 7.40-7.2 (m, 5H, ArH); 7.05 (s, 1H, N_1H), 4.60 (s, 1H, C_4H), 3.50 (s, 1H, C_5H), 1.97 (s, 3H, $COCH_3$), and 1.02 (s, 3H, CH_3).
4c	290.2 (100, M^+)	(DMSO-d_6): 9.40 (s, 1H, N_1H), 7.9 (d, 1H, N_3H); 7.74 (t, 1H, $C_3'H$); 7.70 (d, 1H, $C_4'H$), 7.60 (d, 1H, $C_6'H$); 7.52 (t, 1H, $C_5'H$); 5.9 (d, 1H, C_4H), 2.36 (s, 3H, $COCH_3$) and 2.10 (s, 3H, CH_3)
4d	305 (12, M^+), 165 (100)	(DMSO-d_6): 6.98-6.92 (overlapped singlet and doublet, 3H, ArH), 6.83, 6.82 (2s, 2H, 2NH), 4.59 (s, 1H, C_4H), 3.74 (s, 6H, 2 OCH_3), 3.69 (s, 1H, C_5H), 1.96 (s, 3H, $COCH_3$), and 1.1 (s, 3H, CH_3)
4e	335 (32, M^+), & 195 (100)	(DMSO-d_6): 7.03 (s, 1H, N_1H), 6.99 (s, 1H, N_3H), 6.66 (s, 2H, C2′& $C_6'H$), 4.59 (s, 1H, C_4H), 3.75 (s, 6H, 2OCH_3), 3.65 (s, 1H, C_5H), 3.63 (s, 3H, OCH_3), 1.95 (s, 3H,$COCH_3$) and 1.13 (s, 3H, CH_3)
4f	291 (18, M^+), 274 (100, M^+-OH)	(DMSO-d_6): 8.84 (s, 1H, OH), 6.98 (d, 1H, N_1H), 6.93 (d, 2H, NH^3 + $C_2'H$), 6.7 (2d, 2H, C_5' & $C_6'H$), 4.54 (t, 1H, C_4H), 3.75 (s, 3H, OCH_3), 3.64 (s, 1H, C_5H), 1.95 (s, 3H, $COCH_3$), and 1.11 (s, 3H, CH_3).
4g	307.1 (100, M^+)	(DMSO-d_6): 8.99 (s, 1H, NH), 8.63 (s, 1H, OH), 6.92 (s, 1H, NH), 6.85 (s, 1H, $C_2'H$), 6.69 (d,1H, C5′-H), 6.60 (d, $C_6'H$), 5.52 (d, 1H, C_4H), 3.92 (s, 3H, OCH_3), 3.60 (s, 1H, C_5H), 1.95 (s, 3H, $COCH_3$), and 1.05 (s, 3H, CH_3)
5a	261(8, M^+) & 189 (100)	(DMSO-d_6): 9.75 (s, 1H, OH), 7.11 (t, 1H, ArH), 7.01 (2s, 2H, N_1H and N_3H), 6.83 (m, 3H, Ar-Hs), 4.77 (d, 1H, C4-H), 1.96 (s, 3H, CH_3), 1.06 (s, 3H, CH_3)

Contd

Table III — ^{1}H NMR and mass spectra of the prepared compounds — *Contd*

Compd	Mass spectra MS, m/z, (%)	^{1}H NMR, δ, ppm
5b	291 (8, M^+), 189 (100)	(DMSO-d_6): 8.9 (s, 1H, OH), 7.11 (d, 1H, N_3H), 6.9 (d, 1H, ArH), 6.8 (t, 1H, ArH), 6.62 (d, 1H, ArH), 4.8 (d, 1H, C_4H), 4.8 (s, 3H, OCH_3), 3.5 (s, 1H, C_5H), 1.96 (s, 3H, CH_3), 1.06 (s, 3H, CH_3)
6a	244.3 (29, M^+), 187 (18, M^+ - [C(Me)= NNH_2]) & 97 (100)	(DMSO-d_6): 11.99 (s, 1H, N_1H), 7.29 (t, 2H, ArH-$C_3'C_4'$), 7.18 (m, 3H, $C_2'C_5'C_6'$-H), 6.47 (d, 1H, N_3H), 5.82 (d, 1H, C_4H), 5.52 (s, 2H, NH_2), 1.94 (s, 6H, $2CH_3$)
6b	334 (22, M^+), 317 (56, M^+-OH), 166 (100)	(DMSO-d_6): 11.96 (s, 1H, N_1H), 6.62 (s, 3H, 1H for N_3H + 2H-$C_2'C_6'$), 5.83 (d, 1H, C_4H), 5.49 (s, 2H, NH_2), 3.69 (s, 6H, 2-OCH_3), 3.61 (s, 3H, OCH_3) and 1.94 (s, 6H, $2CH_3$).
6c	290.1 (15, M^+), & 152 (100)	(DMSO-d_6): 11.99 (b, 1H, N^1H), 8.80 (b, 1H, OH), 6.72 (m, 2H, C5′C6′-Hs), 6.57 (d, 1H, C2′-H), 6.40 (d, 1H, NH^3), 5.73 (d, (d, 1H, C4-H), 5.46 (s, 2H, NH_2), 3.69 (s, 3H, OCH_3), and 1.85 (s, 6H, $2CH_3$).
7	304.1 (12, M^+), 165, 208 (100).	(DMSO-d_6): 12.0 (br, 1H, N_1H), 6.92, (m, 3H, ArH), 6.98 (d, 1H, N_3H), 5.78 (t, 1H, C_4H), 3.72 (d, 6H, $2OCH_3$), 3.21 (d, 1H, C_5H), 1.87 (s, 3H, CH_3) and 0.9 (s, 3H, CH_3).
8	290.1 (9, M^+), 230, 194, & 152 (100)	(DMSO-d_6): 8.85, (s, 1H, OH), 6.90 (d, 1H, ArH), 6.77 (t, 1H, ArH), 6.65 (d, 1H, ArH), 6.14 (s, 1H, N_1H), 5.97 (d, 1H, N_3H), 4.86 (s, 1H, C_4H), 3.79 (s, 3H, OCH_3), 3.11 (s, 1H, C_5H), 1.88 (s, 3H, CH_3) and 0.89 (s, 1H, CH_3).

General procedure for preparation of 4-aryl-3,7a-dimethyl-4,5,7,7a-tetrahydro-3a*H* - isoxazolo-[5,4-*d*]pyrimidin-6-one(thione), 4a-g, 5a and 5b. A mixture of the acetyl derivative (10 mmoles) dissolved in ethyl alcohol (30 mL), hydroxyl amine hydrochloride (1.0 g, 15 mmoles) and sodium acetate (1.5 g) was heated under reflux for several hr until completion of the reaction (4-12 hr, monitored by TLC). The solvent was removed under reduced pressure and the residual product was treated with 50 mL water and filtered, washed with water, dried and crystallized.

General procedure for preparation of 4-aryl-5-(1-hydrazonoethyl)-6-methyl-3,4- dihydro-1*H*-pyrimidin-2-one 6a-c and 4-aryl-3,7a-dimethyl-1,3a,4,5, 7, 7a-hexahydropyrazolo[3,4-*d*]-pyrimidin-6-one, 7 and 8. To a solution of the acetyl derivative (10 mmoles) dissolved in dioxane (30 mL) was added hydrazine hydrate (2 mL) and the mixture was heated under reflux for several hr until completion of the reaction (4-12 hr, monitored by TLC). The solvent was removed under reduced pressure and the residual product was treated with 50 mL water and filtered, washed with water, dried then crystallized from the proper solvent.

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