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Regiospecific one-pot, combinatorial synthesis of new substituted pyrimido[4,5-*c*]pyridazines as potential monoamine oxidase inhibitors

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Abstract: New 3-aryl-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and 3-aryl-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones were efficiently synthesized via a regiospecific one-pot reaction of *N*-methylbarbituric acid and *N*-ethyl-2-thiobarbituric acid with various arylglyoxal monohydrates in the presence of hydrazine dihydrochloride in ethanol at 50 °C. The target compounds were obtained in high yields and were regioisomerically pure after recrystallization. These new heterocycles may act as potential MAO$_B$ inhibitors.

Key words: Pyrimido[4,5-*c*]pyridazine, regiospecific, arylglyoxal, *N*-methylbarbituric acid, *N*-ethyl-2-thiobarbituric acid

1. Introduction

Multicomponent reactions (MCRs) are one-pot processes in which three or more reactants come together in a single reaction vessel to form a product containing substantial elements of all the reactants.[1–4] MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for combinatorial chemistry as powerful tools,[5–9] because of their valuable features such as atom economy, environmental friendliness, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diverse elements in a single chemical operation.[10–14] Therefore, a great deal of current interest is focused on the development of novel MCRs.[15]

Substituted pyridazines are valuable therapeutic agents and are the subunits of multiple classes of natural products.[16,17] The synthesis and utility of many pyridazine derivatives as analgesics, insecticidals,[18] fungicidals,[19] cardiotonics,[20] and bacteriocides[21] have been reported. Moreover, fused pyridazines and their derivatives are known to exhibit pharmacological properties, for example, as anti-inflammatory[22] and antibacterial agents,[23] protein tyrosine phosphatase inhibitors,[24] and anticancer agents.[25] In particular, pyrimido[4,5-*c*]pyridazine-5, 7(6*H*, 8*H*)-diones are common sources for the development of new potential therapeutic agents.[26–28] Carotti et al. have reported that the 3-arylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones have MAO inhibitory activity, and substituents on the diazine nucleus modulate the inhibitory activity.[29]

Monoamine oxidase (MAO) is a ubiquitous membrane-bound, flavin-containing enzyme particularly abundant in the liver and brain.[30] In mammals, two distinct isoforms of MAO are present in most tissues,

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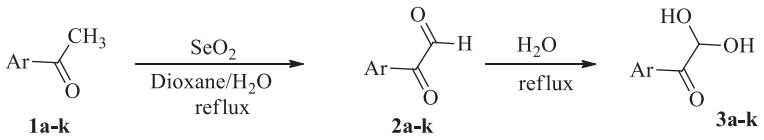
namely, MAO_A and MAO_B, which were defined in 1968, based on their differential substrate and inhibitor specificity,[31−33] tissue and cell distribution,[34] and gene expression[35,36] characteristics.

As such, the development of synthetic methodologies that combine high levels of regiocontrol and flexibility continues to be intensively researched within organic chemistry.

Recently, we have been interested in regioselective one-pot synthesis of various heterocyclic compounds.[37−45] Following our previous reports about the synthesis of 3- or 4-aryl substituted pyrimido[4,5-*c*]pyridazines,[40,43,45] herein we wish to report the synthesis of new substituted pyrimidopyridazines as 3-aryl-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and 3-aryl-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones, which were efficiently prepared via a regiospecific one-pot reaction of *N*-methylbarbituric acid and *N*-ethyl-2-thiobarbituric acid with various arylglyoxal monohydrates in the presence of hydrazine dihydrochloride in ethanol.

2. Results and discussion

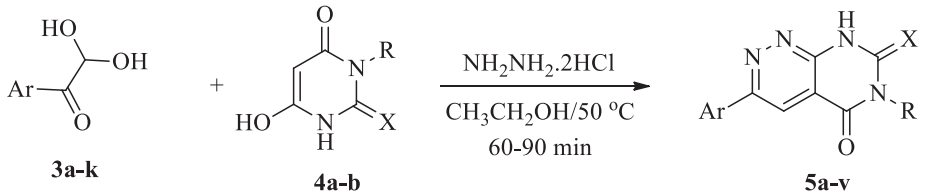
Recently, glyoxals have attracted much attention in heterocyclic synthetic chemistry.[46] They can be prepared from the corresponding acetophenones via oxidation by SeO_2 in dioxane in reflux conditions.[47] In order to protect the arylglyoxals from oxidation and polymerization, these compounds were converted to their monohydrate isomers. The synthesis of the utilized arylglyoxal monohydrates is shown in Scheme 1.



Ar= Phenyl, 4-Bromophenyl, 4-Chlorophenyl, 4-Fluorophenyl, 4-Methoxyphenyl, 4-Nitrophenyl, 3-Bromophenyl, 3-Methoxyphenyl, 3,4-Dimethoxyphenyl, 4-Hydroxy-3-methoxyphenyl, 3,4-Methylenedioxyphenyl

Scheme 1. Synthesis of arylglyoxal monohydrates.

As shown in Scheme 2, arylglyoxal monohydrates **3a**–**k** were reacted with *N*-methylbarbituric acid **4a** or *N*-ethyl-2-thiobarbituric acid **4b** in the presence of hydrazine dihydrochloride salt in ethanol at 50 °C, leading to the formation of pyrimidopyridazines **5a**–**v** in moderate to good yields.



Ar= Phenyl, 4-Bromophenyl, 4-Chlorophenyl, 4-Fluorophenyl, 4-Methoxyphenyl, 4-Nitrophenyl, 3-Bromophenyl, 3-Methoxyphenyl, 3,4-Dimethoxyphenyl, 4-Hydroxy-3-methoxyphenyl, 3,4-Methylenedioxyphenyl
R=CH_3, CH_3CH_2
X=O, S

Scheme 2. Synthesis of 3-aryl-6-alkylpyrimido[4,5-*c*]pyridazine derivatives.

The structures of all twenty-two new examples of these substituted pyrimido[4,5-*c*]pyridazines are shown in the Table.

Table. List of synthesized substituted pyrimido[4,5-*c*]pyridazines.

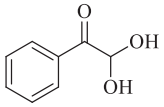
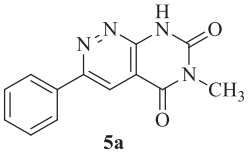
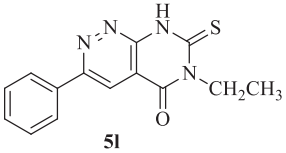
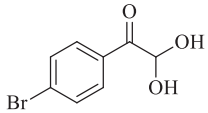
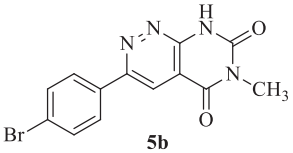
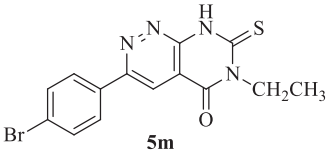
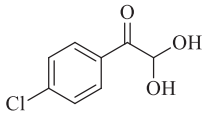
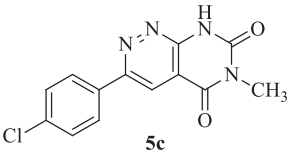
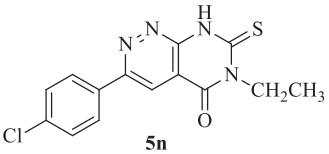
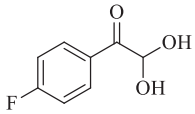
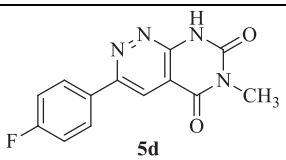
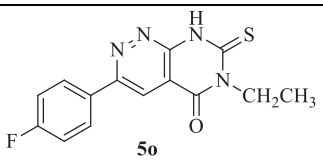
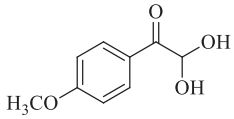
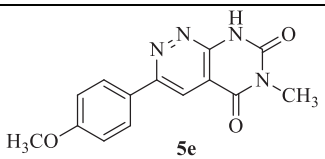
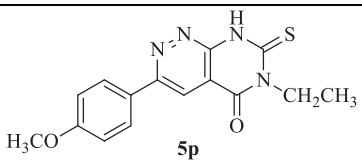
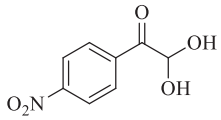
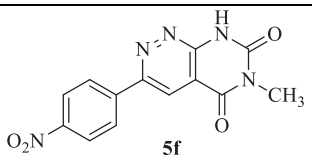
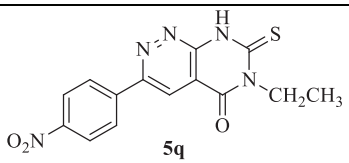
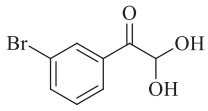
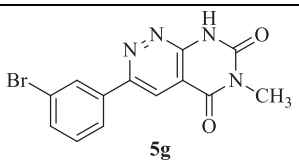
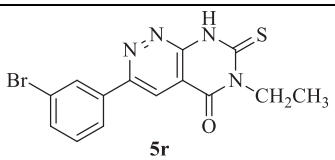
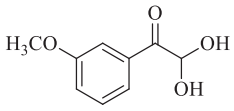
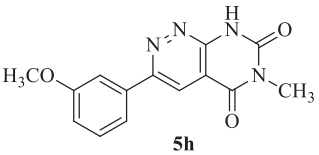
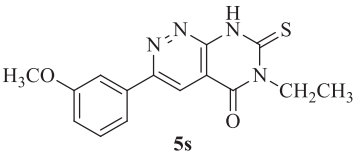
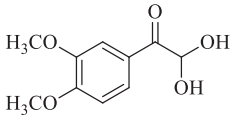
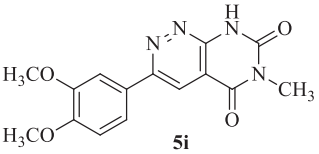
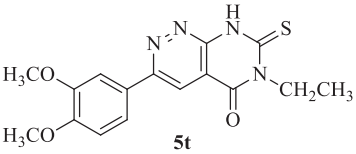
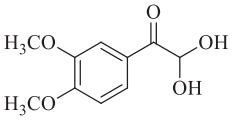
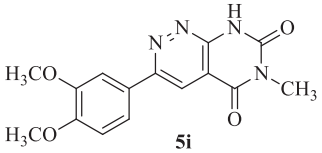
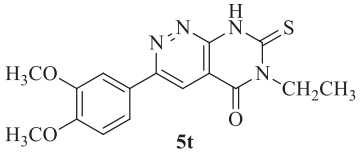
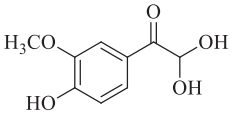
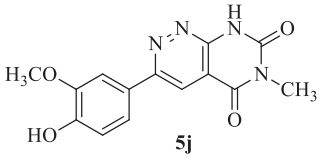
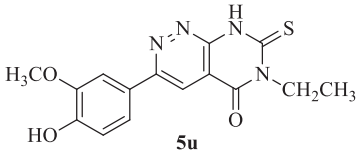
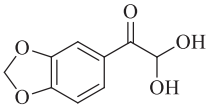
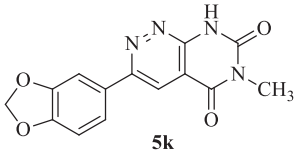
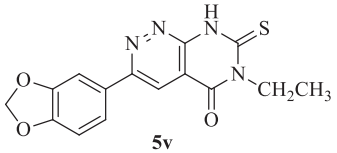
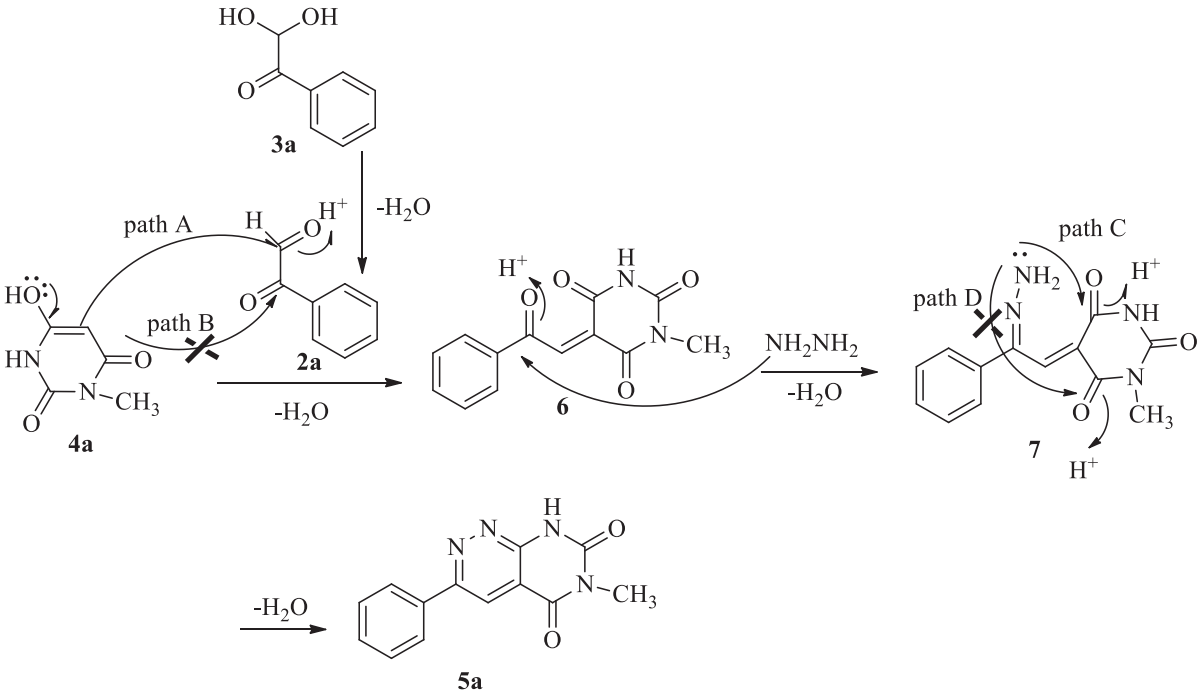
Entry	Arylglyoxal monohydrate	3-Aryl-6-methylpyrimidopyridazine	3-Aryl-6-ethylpyrimidopyridazine
1	 **3a**	 **5a**	 **5l**
2	 **3b**	 **5b**	 **5m**
3	 **3c**	 **5c**	 **5n**
4	 **3d**	 **5d**	 **5o**
5	 **3e**	 **5e**	 **5p**
6	 **3f**	 **5f**	 **5q**
7	 **3g**	 **5g**	 **5r**
8	 **3h**	 **5h**	 **5s**
9	 **3i**	 **5i**	 **5t**

Table. Continued

Entry	Arylglyoxal monohydrate	3-Aryl-6-methylpyrimidopyridazine	3-Aryl-6-ethylpyrimidopyridazine
9	 **3i**	 **5i**	 **5t**
10	 **3j**	 **5j**	 **5u**
11	 **3k**	 **5k**	 **5v**

Attempts to synthesize the desired pyrimidopyridazines by using hydrazinium hydroxide instead of hydrazine dihydrochloride failed. All new products were characterized as 3-aryl substituted pyrimidopyridazines and there was no evidence of the formation of 4-aryl substituted isomers. This is due to initial regioselective Knoevenageal condensation between hydrated carbonyl of the arylglyoxal monohydrates and barbituric acids (path A). Furthermore, because of regiospecific condensation of the hydrazone intermediate **7** and the carbonyl located in position 4 of the barbituric acids, both CH_3 and CH_3CH_2 groups were located in position 6 of the pyrimidopyridazine rings (path C). The suggested mechanism for these reactions is shown in Scheme 3.



Scheme 3. Proposed mechanism for regiospecific synthesis of 3-aryl-6-alkylpyrimidopyridazine derivatives.

We have previously reported that 3-arylpyrimido[4, 5-*c*]pyridazine-5, 7(6*H*, 8*H*)-diones and 3-aryl-7-thioxo-7, 8-dihydropyrimido[4, 5-*c*]pyridazin-5(6*H*)-ones can have one cluster water in their molecular structure.[48] As outlined from the ^{1}H NMR spectra of 3-aryl-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones and 3-aryl-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones, there is no evidence of the existence of cluster water in the molecular structure of these compounds. This phenomenon may be because of the presence of methyl or ethyl groups, which prevent the formation of hydrogen bonding between water and the amide group.

According to Carotti and coworkers' report about the MAO$_B$ inhibitory property of 3-arylsubstituted pyrimido[4,5-*c*]pyridazines,[29] we speculated that the synthesis of various aryl and alkyl substituted pyrimidopyridazines as potential MAO$_B$ inhibitors may change the MAO inhibitory effect of these derivatives. The corresponding biological activity of all the new substituted 3-arylpyrimido[4,5-*c*]pyridazine-5, 7(6*H*, 8*H*)-diones and 3-aryl-7-thioxo-7, 8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-ones is under assessment.

3. Experimental

3.1. General procedures

All chemicals were purchased from Merck, Aldrich, and Acros. Melting points were determined on an Electrothermal 9200 apparatus. Infrared spectra were recorded on a PerkinElmer Spectrum Two 10.4 spectrometer, using KBr discs. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE (300 MHz) spectrometer using d_6-DMSO as solvent. Microanalyses were performed on a Leco Analyzer *932*.

3.2. General procedure for the synthesis of 3-aryl-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-diones

A mixture of *N*-methylbarbituric acid (1 mmol) and arylglyoxal monohydrate (1 mmol) in the presence of hydrazine dihydrochloride (1 mmol) in absolute ethanol (10 mL) was heated at 50 °C for 60 min. The obtained precipitate was separated by filtration and washed with excess rectified spirit. The crude products were recrystallized from methanol to give the title compounds in good yields.

3.2.1. 3-Phenyl-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5a)

A white powder, 78%, mp 271 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.59 (s, 1H, NH), 8.47 (s, 1H, Ar), 8.18 (d, J = 8.0 Hz, 2H, Ar), 7.60–7.49 (m, 3H, Ar), 3.26 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.3, 155.4, 151.1, 135.3, 130.3, 129.8, 129.1, 127.9, 126.4, 121.5, 27.4. FT-IR (KBr) ν_{max} 3190, 1727, 1663, 1483, 1368, 1296, 1049, 762, 693 cm^{-1}. Anal. found, C, 61.47; H, 3.98; N, 22.11. $C_{13}H_{10}N_4O_2$ requires C, 61.41; H, 3.96; N, 22.04.

3.2.2. 3-(4-Bromophenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5b)

A gray powder, 82%, mp 275 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.61 (s, 1H, NH), 8.52 (s, 1H, Ar), 8.15 (d, J = 7.8 Hz, 1H, Ar), 7.73 (d, J = 7.8 Hz, 1H, Ar), 3.27 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.2, 154.4, 151.2, 150.0, 134.5, 132.0, 123.5, 123.4, 121.5, 113.3, 27.4. FT-IR (KBr) ν_{max} 3175, 1736, 1662, 1615, 1481, 1447, 1364, 1297, 1047, 828 cm^{-1}. Anal. found, C, 46.80; H, 2.62; N, 16.91. $C_{13}H_9BrN_4O_2$ requires C, 46.87; H, 2.72; N, 16.82.

3.2.3. 3-(4-Chlorophenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5c)

A gray powder, 86%, mp 279 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.63 (s, 1H, NH), 8.83 (s, 1H, Ar), 8.23 (d, J = 8.6 Hz, 2H, Ar), 7.61 (d, J = 8.5 Hz, 2H, Ar), 3.27 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.2, 154.3, 151.2, 150.1, 134.7, 134.2, 129.1, 128.3, 121.6, 113.3, 27.5. FT-IR (KBr) ν_{max} 3178, 1739, 1661, 1615, 1482, 1447, 1365, 1297, 1093, 831 cm^{-1}. Anal. found, C, 54.01; H, 3.10; N, 19.61. $C_{13}H_9ClN_4O_2$ requires C, 54.09; H, 3.14; N, 19.41.

3.2.4. 3-(4-Fluorophenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5d)

A white powder, 80%, mp 257 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.59 (s, 1H, NH), 8.50 (s, 1H, Ar), 8.26–8.23 (m, 2H, Ar), 7.39–7.35 (m, 2H, Ar), 3.27 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 164.4, 162.0, 161.2, 154.5, 151.0, 150.0, 131.8, 128.8, 128.7, 121.4, 116.1, 115.8, 113.3, 27.4. FT-IR (KBr) ν_{max} 3195, 3053, 1722, 1671, 1604, 1489, 1366, 1230, 836 cm^{-1}. Anal. found, C, 57.40; H, 3.38; N, 20.68. $C_{13}H_9FN_4O_2$ requires C, 57.35; H, 3.33; N, 20.58.

3.2.5. 3-(4-Methoxyphenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5e)

A yellow powder, 85%, mp 253 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.52 (s, 1H, NH), 8.81 (s, 1H, Ar), 8.13 (d, J = 8.6 Hz, 2H, Ar), 7.08 (d, J = 8.6 Hz, 2H, Ar), 3.83 (s, 3H, OCH_3), 3.26 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.4, 155.2, 150.6, 132.0, 129.3, 128.0, 127.9, 127.7, 120.7, 114.5, 55.3, 27.5. FT-IR (KBr) ν_{max} 3198, 2931, 1729, 1666, 1609, 1490, 1296, 1252, 1176, 1176, 1032, 839, 747 cm^{-1}. Anal. found, C, 59.18; H, 4.24; N, 19.80. $C_{14}H_{12}N_4O_3$ requires C, 59.15; H, 4.25; N, 19.71.

3.2.6. 3-(4-Nitrophenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5f)

A yellow powder, 79%, mp 281 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.84 (s, 1H, NH), 8.93 (s, 1H, Ar), 8.45 (d, J = 8.5 Hz, 2H, Ar), 7.89 (d, J = 8.5 Hz, 2H, Ar), 3.45 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.4, 155.2, 150.6, 132.0, 129.3, 128.0, 127.9, 127.7, 120.7, 114.5, 55.3, 27.5. FT-IR (KBr) ν_{max} 3203, 2954, 1754, 1675, 1567, 1358, 839, 747 cm^{-1}. Anal. found, C, 52.25; H, 3.06; N, 23.55. $C_{13}H_9N_5O_4$ requires C, 52.18; H, 3.03; N, 23.40.

3.2.7. 3-(3-Bromophenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5g)

A cream powder, 75%, mp 254 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.65 (bs, 1H, NH), 8.59 (s, 1H, Ar), 8.40 (s, 1H Ar), 8.21 (d, J = 7.9 Hz, 1H, Ar), 7.72 (d, J = 7.9 Hz, 1H, Ar), 7.51 (t, J = 7.9 Hz, 1H, Ar), 3.27 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.2, 153.9, 151.5, 150.1, 137.6, 132.4, 131.2, 129.1, 129.0, 122.5, 122.0, 113.3, 27.5. FT-IR (KBr) ν_{max} 3183, 1737, 1661, 1564, 1500, 1450, 1367, 1295, 1193, 1050, 790 cm^{-1}. Anal. found, C, 46.89; H, 2.67; N, 16.99. $C_{13}H_9BrN_4O_2$ requires C, 46.87; H, 2.72; N, 16.82.

3.2.8. 3-(3-Methoxyphenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5h)

A yellow powder, 90%, mp 258 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.70 (s, 1H, NH), 8.47 (s, 1H, Ar), 7.94–7.84 (m, 4H, Ar), 3.85 (s, 3H, OCH_3), 3.26 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ

(ppm) 159.8, 159.2, 158.1, 156.2, 146.7, 138.6, 137.0, 135.2, 130.1, 129.6, 120.2, 113.6, 55.1, 27.6. FT-IR (KBr) ν_{max} 3091, 2933, 1659, 1583, 1482, 1359, 1273, 1230, 1047, 781 cm^{-1}. Anal. found, C, 59.18; H, 4.24; N, 19.80. $C_{14}H_{12}N_4O_3$ requires C, 59.15; H, 4.25; N, 19.71.

3.2.9. 3-(3,4-Dimethoxyphenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5i)

A yellow powder, 88%, mp 251 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.51 (s, 1H, NH), 8.45 (s, 1H, Ar), 7.73 (s, 1H, Ar), 7.71 (d, J = 8.2 Hz, 1H, Ar), 7.08 (d, J = 8.0 Hz, 1H, Ar), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.26 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.3, 155.2, 150.6, 149.1, 129.9, 127.8, 127.5, 120.9, 119.3, 113.2, 111.8, 109.4, 55.6, 55.5, 27.4. FT-IR (KBr) ν_{max} 3108, 3088, 2933, 1734, 1679, 1595, 1501, 1457, 1386, 1263, 1148, 1023, 794 cm^{-1}. Anal. found, C, 57.27; H, 4.45; N, 17.98. $C_{15}H_{14}N_4O_4$ requires C, 57.32; H, 4.49; N, 17.83.

3.2.10. 3-(4-Hydroxy-3-methoxyphenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5j)

An orange powder, 92%, mp 249 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.52 (bs, 1H, NH), 9.48 (bs, 1H, OH), 8.41 (s, 1H, Ar), 7.82 (s, 1H, Ar), 7.80 (d, J = 7.6 Hz, 1H, Ar), 6.91 (dd, J_1 = 8.4 Hz, J_2 = 2.9 Hz, 1H, Ar), 3.88 (s, 3H, OCH_3), 3.25 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.4, 156.3, 155.5, 153.2, 150.4, 148.5, 128.7, 126.5, 119.6, 115.8, 113.2, 110.0, 55.7, 27.4. FT-IR (KBr) ν_{max} 3430, 1728, 1674, 1567, 1451, 1383, 1275, 1217, 1124, 1033, 791 cm^{-1}. Anal. found, C, 56.09; H, 4.10; N, 18.77. $C_{14}H_{12}N_4O_4$ requires C, 56.00; H, 4.03; N, 18.66.

3.2.11. 3-(3,4-Methylenedioxyphenyl)-6-methylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione (5k)

A beige powder, 83%, mp 268 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.57 (s, 1H, NH), 8.47 (s, 1H, Ar), 7.86 (d, J = 8.4 Hz, 1H, Ar), 7.83 (s, 1H, Ar), 7.03 (dd, J_1 = 7.6 Hz, J_2 = 3.2 Hz, 1H, Ar), 6.12 (s, 2H, CH_2), 3.25 (s, 3H, NCH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.4, 156.1, 152.8, 148.7, 148.1, 129.0, 128.8, 125.1, 122.2, 116.2, 110.5, 101.3, 27.4. FT-IR (KBr) ν_{max} 3100, 2902, 1673, 1580, 1482, 1448, 1237, 1037, 930, 810 cm^{-1}. Anal. found, C, 56.43; H, 3.33; N, 18.92. $C_{14}H_{10}N_4O_4$ requires C, 56.38; H, 3.38; N, 18.78.

3.3. General procedure for the synthesis of 3-aryl-6-ethyl-7-thioxo-7, 8-dihydropyrimido[4,5-*c*]pyridazine-5(6*H*)-ones

A mixture of *N*-ethyl-2-thiobarbituric acid (1 mmol) and arylglyoxal monohydrate (1 mmol) in the presence of hydrazine dihydrochloride (1 mmol) in absolute ethanol (10 mL) was heated at 50 °C for 90 min. The obtained precipitate was separated by filtration and washed with excess rectified spirit. The crude products were purified via recrystallization from methanol.

3.3.1. 3-Phenyl-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5l)

An orange powder, 80%, mp 218 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 12.15 (s, 1H, NH), 8.50 (s, 1H, Ar), 8.01 (d, J = 7.8 Hz, 2H, Ar), 7.80 (t, J = 7.2 Hz, 1H, Ar), 7.55 (t, J = 7.2 Hz, 2H, Ar), 4.43 (q, J = 7.2 Hz, 2H, CH_2), 1.23 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 176.4, 159.1, 145.1, 142.5, 135.1, 130.2, 129.6, 127.0, 121.2, 114.8, 41.3, 11.6. FT-IR (KBr) ν_{max} 3191, 3059, 2931,

2829, 1679, 1620, 1559, 1454, 1346, 1205, 1112, 1087, 688 cm^{-1}. Anal. found, C, 59.16; H, 4.21; N, 19.84; S, 11.34. $C_{14}H_{12}N_4OS$ requires C, 59.14; H, 4.25; N, 19.70; S, 11.28.

3.3.2. 3-(4-Bromophenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5m)

A brown powder, 72%, mp 221 °C (dec.). ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.65 (s, 1H, NH), 8.65 (s, 1H, Ar), 8.47 (d, J = 8.7 Hz, 2H, Ar), 7.78 (d, J = 8.7 Hz, 2H, Ar), 4.38 (q, J = 6.9 Hz, 2H, CH_2), 1.19 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 161.7, 154.0, 148.2, 143.9, 141.1, 128.3, 127.8, 124.2, 121.5, 113.9, 71.4, 11.5. FT-IR (KBr) υ_{max} 3179, 3048, 2979, 2932, 1681, 1605, 1591, 1568, 1523, 1489, 1443, 1343, 1236, 1108, 829 cm^{-1}. Anal. found, C, 46.30; H, 3.01; N, 15.57; S, 8.91. $C_{14}H_{11}BrN_4OS$ requires C, 46.29; H, 3.05; N, 15.42; S, 8.83.

3.3.3. 3-(4-Chlorophenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5n)

A brown powder, 79%, mp 232 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.95 (s, 1H, NH), 8.55 (s, 1H, Ar), 8.25 (d, J = 8.5 Hz, 2H, Ar), 7.61 (d, J = 8.5 Hz, 2H, Ar), 4.43 (q, J = 6.6 Hz, 2H, CH_2), 1.23 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 176.6, 158.8, 135.0, 134.1, 129.2, 128.6, 128.5, 127.3, 121.5, 114.9, 41.4, 11.7. FT-IR (KBr) υ_{max} 3180, 3068, 2980, 2896, 1680, 1569, 1524, 1492, 1444, 1344, 1236, 1109, 1096, 832 cm^{-1}. Anal. found, C, 52.81; H, 3.44; N, 17.69; S, 10.10. $C_{14}H_{11}ClN_4OS$ requires C, 52.75; H, 3.48; N, 17.58; S, 10.06.

3.3.4. 3-(4-Fluorophenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5o)

A yellow powder, 71%, mp 225 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.93 (s, 1H, NH), 8.53 (s, 1H, Ar), 8.30–8.25 (m, 2H, Ar), 7.40–7.35 (m, 2H, Ar), 4.41 (q, J = 6.9 Hz, 2H, CH_2), 1.23 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 173.2, 158.7, 155.6, 131.6, 130.0, 129.0, 128.9, 121.2, 116.2, 115.9, 114.8, 92.9, 12.2. FT-IR (KBr) υ_{max} 3185, 3081, 2981, 2895, 1709, 1675, 1634, 1597, 1555, 1507, 1443, 1344, 1236, 1111, 839 cm^{-1}. Anal. found, C, 55.68; H, 3.61; N, 18.68; S, 10.69. $C_{14}H_{11}FN_4OS$ requires C, 55.62; H, 3.67; N, 18.53; S, 10.61.

3.3.5. 3-(4-Methoxyphenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5p)

A yellow powder, 75%, mp 268 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.88 (s, 1H, NH), 8.41 (s, 1H, Ar), 8.15 (d, J = 8.7 Hz, 2H, Ar), 7.10 (d, J = 7.2 Hz, 2H, Ar), 4.42 (q, J = 6.9 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 1.22 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 160.4, 158.8, 144.8, 132.0, 128.6, 127.5, 126.9, 120.3, 114.7, 112.4, 81.7, 55.2, 11.6. FT-IR (KBr) υ_{max} 3185, 3071, 2984, 2888, 1678, 1609, 1570, 1502, 1452, 1363, 1250, 1178, 1106, 1031, 831 cm^{-1}. Anal. found, C, 57.33; H, 4.46; N, 17.99; S, 10.27. $C_{15}H_{14}N_4O_2S$ requires C, 57.31; H, 4.49; N, 17.82; S, 10.20.

3.3.6. 3-(4-Nitrophenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5q)

A brown powder, 73%, mp 181 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 14.05 (s, 1H, NH), 8.71 (s, 1H, Ar), 8.52 (d, J = 9.0 Hz, 2H, Ar), 8.38 (d, J = 9.0 Hz, 2H, Ar), 4.44 (q, J = 7.2 Hz, 2H, CH_2), 1.23 (t, J = 6.6 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 158.6, 154.0, 148.2, 144.5, 141.1, 128.3, 127.8, 124.2, 122.5, 114.8, 72.8, 11.5. FT-IR (KBr) υ_{max} 3182, 3062, 2985, 2898, 1678, 1605, 1518, 1494, 1445, 1343,

1235, 1106, 856 cm^{-1}. Anal. found, C, 51.08; H, 3.40; N, 21.39; S, 9.80. $C_{14}H_{11}N_5O_3S$ requires C, 51.06; H, 3.37; N, 21.27; S, 9.74.

3.3.7. 3-(3-Bromophenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5r)

A beige powder, 75%, mp 188 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.96 (s, 1H, NH), 8.55 (s, 1H, Ar), 8.40 (s, 1H, Ar), 8.21 (d, J = 7.8 Hz, 1H, Ar), 7.71–7.65 (m, 2H, Ar), 4.41 (q, J = 6.9 Hz, 2H, CH_2), 1.22 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 158.7, 154.6, 137.5, 136.1, 132.7, 132.6, 131.3, 129.2, 128.5, 125.7, 122.6, 121.9, 41.4, 11.9. FT-IR (KBr) υ_{max} 3184, 3095, 2988, 2887, 1681, 1651, 1669, 1564, 1518, 1452, 1343, 1239, 1110, 1087, 793, 737 cm^{-1}. Anal. found, C, 46.23; H, 3.09; N, 15.59; S, 8.90. $C_{14}H_{11}BrN_4OS$ requires C, 46.29; H, 3.05; N, 15.42; S, 8.83.

3.3.8. 3-(3-Methoxyphenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5s)

A yellow powder, 73%, mp 251 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.93 (s, 1H, NH), 8.51 (s, 1H, Ar), 7.76–7.72 (m, 2H, Ar), 7.44 (t, J = 8.1 Hz, 1H, Ar), 7.06 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1 H, Ar), 4.42 (q, J = 6.9 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3), 1.22 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 176.5, 160.0, 158.8, 155.9, 150.5, 136.6, 130.3, 121.5, 119.0, 116.1, 114.8, 111.5, 55.4, 41.4, 11.7. FT-IR (KBr) υ_{max} 3196, 3092, 2988, 1680, 1609, 1495, 1452, 1342, 1238, 1129, 1104, 1032, 793, 741 cm^{-1}. Anal. found, C, 57.36; H, 4.41; N, 17.91; S, 10.24. $C_{15}H_{14}N_4O_2S$ requires C, 57.31; H, 4.49; N, 17.82; S, 10.20.

3.3.9. 3-(3,4-Dimethoxyphenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5t)

A gray powder, 79%, mp 228 °C (dec.). ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 3.54 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 7.01 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 8.46 (s, 1H). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 160.6, 156.1, 151.3, 150.3, 149.9, 127.4, 121.6, 119.5, 113.8, 111.3, 109.3, 56.1, 56.0, 29.9, 28.9. FT-IR (KBr) υ_{max} 3151, 3082, 2996, 2834, 1701, 1656, 1601, 1585, 1521, 1513, 1437, 1347, 1234, 1148, 1108, 1022, 885, 793 cm^{-1}. Anal. found, C, 55.85; H, 4.72; N, 16.36; S, 9.37. $C_{16}H_{16}N_4O_3S$ requires C, 55.80; H, 4.68; N, 16.27; S, 9.31.

3.3.10. 3-(4-Hydroxy-3-methoxyphenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5(6*H*)-one (5u)

An orange powder, 70%, mp 269 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.85 (s, 1H, NH), 9.53 (s, 1H, OH), 8.44 (s, 1H, Ar), 7.75 (s, 1H, Ar), 7.65 (dd, J_1 = 8.3 Hz, J_2 = 1.8 Hz, 1H, Ar), 6.91 (d, J = 8.3 Hz, 1H, Ar), 4.43 (q, J = 6.9 Hz, 2H, CH_2), 3.88 (s, 3H, OCH_3), 1.22 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 176.0, 158.8, 156.1, 149.8, 148.7, 148.1, 126.3, 120.3, 119.8, 115.9, 114.7, 110.1, 55.7, 41.3, 11.6. FT-IR (KBr) υ_{max} 3294, 3082, 1673, 1615, 1600, 1518, 1432, 1347, 1285, 1262, 1222, 1110, 1090 cm^{-1}. Anal. found, C, 54.61; H, 4.29; N, 17.11; S, 9.79. $C_{15}H_{14}N_4O_3S$ requires C, 54.53; H, 4.27; N, 16.96; S, 9.71.

3.3.11. 3-(3,4-Methylenedioxyphenyl)-6-ethyl-7-thioxo-7,8-dihydropyrimido[4,5-*c*]pyridazin-5 (6*H*)-one (5v)

A beige powder, 77%, mp 262 °C (dec.), ^{1}H NMR (d_6-DMSO, 300 MHz) δ (ppm) 13.53 (s, 1H, NH), 8.42 (s, 1H, Ar), 7.79 (d, J = 8.7 Hz, 1H, Ar), 7.74 (s, 1H, Ar), 7.01 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H, Ar), 6.09 (s, 2H, CH_2), 3.28 (q, J = 6.9 Hz, 2H, CH_2), 1.43 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (d_6-DMSO, 75 MHz) δ (ppm) 171.4, 166.1, 153.8, 148.7, 148.1, 129.0, 127.8, 124.9, 121.8, 117.1, 111.3, 101.1, 49.4, 11.8. FT-IR (KBr) υ_{max} 3106, 2987, 1675, 1585, 1488, 1473, 1239, 1043, 850 cm^{-1}. Anal. found, C, 54.90; H, 3.69; N, 17.21; S, 9.85. $C_{15}H_{12}N_4O_3S$ requires C, 54.87; H, 3.68; N, 17.06; S, 9.77.

4. Conclusions

In summary, we have reported a one-pot reaction for the efficient synthesis of new substituted pyrimido[4,5-*c*]pyridazine derivatives as potential MAO$_B$ inhibitors. By using different types of arylglyoxal monohydrates and barbituric acid derivatives, we obtained novel libraries of pyrimido[4,5-*c*]pyridazine derivatives, which make this methodology suitable for combinatorial and parallel synthesis. The proposed reactions proceed in mild conditions and give the products in good yields with high regiospecificity. The separation and purification processes are very simple and convenient, only needing recrystallization. The starting materials are inexpensive and commercially available.

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