Synthesis of Some Novel Heterocyclic and Schiff Base Derivatives as Antimicrobial Agents

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Academic Editor: Wim Dehaen

Received: 5 September 2015 / Accepted: 23 September 2015 / Published: 7 October 2015

Abstract: Treatment of 2,3-diaryl oxirane-2,3-dicarbonitriles 1a–c with different nitrogen nucleophiles, e.g., hydrazine, methyl hydrazine, phenyl hydrazine, hydroxylamine, thiosemicarbazide, and/or 2-amino-5-phenyl-1,3,4-thiadiazole, afforded pyrazole, isoxazole, pyrrolotriazine, imidazolothiadiazole derivatives 2–5, respectively. Reacting pyrazoles 2a–c with aromatic aldehydes and/or methyl glycinate produced Schiff’s bases 7a–d and pyrazolo[3,4-b]-pyrazinone derivative 8, respectively. Treating 7 with ammonium acetate and/or hydrazine hydrate, furnished the imidazolopyrazole and pyrazolotriazine derivatives 9 and 10, respectively. Reaction of 8 with chloroacetic acid and/or diethyl malonate gave tricyclic compound 11 and triketone 12, respectively. On the other hand, compound 1 was reacted with active methylene precursors, e.g., acetylacetone and/or cyclopentanone producing adducts 14a,b which upon fusion with ammonium acetate furnished the 3-pyridone derivatives 15a,b, respectively. Some of newly synthesized compounds were screened for activity against bacterial and fungal strains and most of the newly synthesized compounds showed high antimicrobial activities. The structures of the new compounds were elucidated using IR, 1H-NMR, 13C-NMR and mass spectroscopy.
Keywords: oxirane; pyrazole; isoxazole; pyrazolopyrazine; Schiff bases; pyridones; antimicrobial activities

1. Introduction

2,3-Diaryloxirane-2,3-dicarbonitriles are well-known as important synthetic intermediates [1,2]. The reaction of such compounds with nitrogen and carbon nucleophiles produces many biologically active heterocyclic compounds. For example, substituted pyrazoles are reported to be an important class of compounds in the agricultural and medicinal chemistry fields because of their broad spectrum biological activities [3–6] and they also have anti-cancer effects [7]. Imidazole derivatives act as potent and selective neuropeptide Y Y5 receptor antagonists, having antifungal and antibacterial activity and are used as potential tuberculostatic agents [8–10]. On the other hand, isooxazole derivatives have antifungal activity against Candida albicans, immunological and immunotrophic activities [11–13]. Schiff bases have remarkable complex-forming properties and serve as excellent chelating ligands and have been used as analytical reagents for the spectrophotometric determination of metal ions [14,15]. For the abovementioned properties, and in continuation of our program in synthesis of biologically active heterocyclic compounds [16–26], we decided to use 2,3-diaryloxirane-2,3-dicarbonitrile derivatives 1a–c as a key starting material for the purpose of preparing some novel heterocyclic compounds by reaction with different nitrogen and carbon nucleophiles whereby we synthesized pyrazoles, oxazoles, fused pyrazoles and pyridines, and then study their antimicrobial activity. Most of the newly synthesized compounds were screened in vitro for their antimicrobial activities against different strains of bacteria and fungi. Some of the compounds such as compounds 7a and 7b showed high antibacterial activity similar to or higher than that of the reference compounds, suggesting that they may find use as antibacterial agents.

2. Results and Discussion

2.1. Chemistry

The 2,3-diaryloxirane-2,3-dicarbonitrile derivatives 1a–c were allowed to react with different nitrogen binucleophiles. Thus, compounds 1a–c were treated with hydrazine derivatives (hydrazine hydrate, methyl hydrazine and/or phenyl hydrazine), hydroxylamine hydrochloride, thiosemicarbazide, and/or 2-amino-5-aryl-1,3,4-thiadiazole to afford 3-amino-1-substituted-5,5-diaryl-1H-pyrazol-4(5H)-ones 2a–e, 3-amino-5,5-diarylisoxazol-4(5H)-ones 3a–e, pyrrolo[2,3-e][1,2,4]triazine-3(2H)-thione (4) and imidazo[2,1-b][1,3,4]thiadiazol-5(6H)-one (5), respectively (Scheme 1).
The speculated mechanism for the formation of compound 2 is shown in Scheme 2.

On the other hand, when compound 1 was reacted with hydrazine hydrate in boiling \( n \)-butanol, two products were isolated, one of them was the pyrazolone 2 and the other was identified to be the imidazolopyrazolone 6 (Scheme 3). The structure of 6 was elucidated from its \( ^1 \)H-NMR and \( ^{13} \)C-NMR spectra, which indicate the presence of four aryl groups and two carbonyl groups. The postulated mechanism for the formation of compound 6 is shown in Scheme 3.
Scheme 2. Mechanism for the formation of compound 2.

Scheme 3. Synthetic route for compound 6.

The structures of pyrazolone derivatives 2a–c were supported chemically by their reaction with aromatic aldehydes (namely: benzaldehyde, and p-chlorobenzaldehyde) and/or methyl glycinate, in boiling ethanol, producing the Schiff’s bases 7a–d and the pyrazolo[3,4-b]-pyrazinone derivative 8, respectively (Scheme 4).
The formation of compounds 7a–c takes place through condensation reactions between the carbonyl group of the aldehyde and the amino group of compound 2 (accompanied by loss of a water molecule). The reaction of 2 with methyl glycinate takes place by the attack of the pyrazole amino group on the ester group followed by the removal of a methanol molecule forming the intermediate A, then elimination of a water molecule to form intermediate B which rearranges to the more stable form 8.

Furthermore, the Schiff's bases 7a–c were subjected to reaction with ammonium acetate (fusion at 90 °C) and/or hydrazine hydrate (in boiling ethanol), afforded the imidazolopyrazoles 9a–c and the pyrazolo[3,4-e]1,2,4-triazine derivatives 10a–c, respectively (Scheme 5).
Compounds 9a–c were formed by the formation of the imine C (by condensation of ammonia and the carbonyl group) followed by ring closure via the attack of the imino group on the C=N moiety of the Schiff's base. Similarly, formation of compounds 10a–c occurs by the formation of the hydrazone D followed by ring closure via the attack of the amino group on the Schiff's base C=N.

Treatment of the pyrazolopyrazinone derivative 8 with chloroacetic acid in the presence of phosphorus oxychloride furnished the tricyclic compound 11, while reaction of diethyl malonate with 8 in boiling ethanol produced the triketone 12, which upon refluxing with benzaldehyde in ethanol, afforded the chalcone 13 (Scheme 6).

\[
\text{Ar} = \text{C}_6\text{H}_4-\text{CH}_3-\text{p}
\]

\[
\begin{align*}
\text{Reaction Conditions: (i) ClCH}_2\text{CO}_2\text{H/POCl}_3/\text{reflux 2 h, 55%; (ii) CH}_2(\text{CO}_2\text{C}_2\text{H}_5)_2/\text{ethanol/reflux 4 h, 57%; (iii) PhCHO/ethanol/reflux 6 h, 24%}. \\
\text{Scheme 6. Synthetic routes for compounds 11–13.}
\end{align*}
\]

The present investigation was extended to explore the reactivity of the oxirane derivative 1a towards some carbon nucleophiles. Thus, when compound 1a was refluxed in ethanol with active methylene compounds (namely: acetylacetone, and/or cyclohexanone) in the presence of 50% aqueous NaOH (as a catalyst), the adducts 14a,b were obtained. Cyclization of 14a,b, by fusion with ammonium acetate furnished the 3-pyridone derivatives 15a,b (Scheme 7).
Molecules 2015, 20 18207

Reaction Conditions: (i) Active methylene/NaOH/ethanol/reflux 3 h, 67%–70%; (ii) Ammonium acetate/fusion at 150 °C/2 h, 65%–74%.

Scheme 7. Synthetic routes for compounds 14 and 15.

A plausible mechanism for the formation of compounds 15a,b is illustrated in Scheme 8.

Scheme 8. Mechanism for the formation of compounds 15a,b.

2.2. Antimicrobial Activity

Most of the newly synthesized compounds were screened in vitro for their antimicrobial activities against different strains of bacteria and fungi. The microorganisms used were Staphylococcus aureus (Gram positive), Escherichia coli, Pseudomonas aeruginosa (Gram negative) and Candida albicans (yeast) by using the agar diffusion method [27] to select the most potent compounds.

One mg of each compound was dissolved in dimethyl sulfoxide (DMSO, 1 mL) then made up to 10 mL with sterile water to give a concentration of 100 μg/mL. The bacteria were maintained on nutrient agar media. The efficiency of the tested compounds was compared to that of ampicillin, streptomycin and nystatin.
The agar media was incubated with the different tested microorganisms. After 24–48 h of incubation at 37 °C, DMSO showed no inhibition zones. The diameters of the inhibition zones of the tested compounds were measured. The results are presented in Table 1.

| Synthesized Compounds | Staphylococcus Aureus | Escherichia Coli | Pseudomonas Aeruginosa | Candida Albicans |
|-----------------------|-----------------------|------------------|------------------------|-----------------|
| 2a                    | 19                    | 20               | 21                     | 15              |
| 2b                    | 19                    | 16               | 21                     | 15              |
| 2c                    | 17                    | 18               | 16                     | 11              |
| 4                     | 12                    | 12               | 18                     | 12              |
| 5                     | 12                    | 16               | 18                     | 10              |
| 6a                    | 12                    | 11               | 15                     | 0.0             |
| 7a                    | 18                    | 23               | 22                     | 15              |
| 7b                    | 17                    | 20               | 21                     | 13              |
| 9a                    | 20                    | 17               | 20                     | 21              |
| 9b                    | 11                    | 14               | 10                     | 16              |
| 10a                   | 13                    | 13               | 0.0                    | 15              |
| 12                    | 14                    | 13               | 0.0                    | 11              |
| 13                    | 16                    | 16               | 19                     | 13              |
| 14                    | 15                    | 17               | 21                     | 12              |
| 15                    | 13                    | 12               | 0.0                    | 11              |
| Ampicillin            | 0.0                   | 22               | 0.0                    | 0.0             |
| Streptomycin          | 20                    | 21               | 0.0                    | 0.0             |
| Nystatin              | 0.0                   | 0.0              | 0.0                    | 22              |

Zone of inhibition measured in mm: no activity (0.0), very weak activity (< 7 mm), weak activity (7–10), moderate activity (11–15 mm), strong activity (> 15 mm).

The antimicrobial activity results revealed that most of the tested compounds have moderate to strong activity. The most potent compounds are 7a, 7b and 9a. When these compounds were compared with the reference compounds (ampicillin, streptomycin and nystatin) we found that they have an antimicrobial activity higher or almost equal to them. On the other hand, in comparing the obtained values of antimicrobial activity for our newly synthesized Schiff bases 7a, 7b with similar compounds which were previously reported [28,29], we found that our compounds display higher antimicrobial activity values.

3. Experimental Section

3.1. General Information

All melting points are uncorrected and were determined on a Stuart electric melting point apparatus. The microanalysis were within ±0.4% of theoretical values and were carried out at the Microanalytical Centre, National Research Centre, Cairo, Egypt. IR spectra (KBr) were recorded on a FT-IR 400D infrared spectrometer (New York, USA) using the OMNIC program and are reported as frequency of absorption in cm⁻¹. ¹H-NMR spectra were recorded on a Bruker spectrophotometer (Rheinstetten,
Germany) at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent $\delta = 7.26$ ppm for CDCl$_3$ and $\delta 2.51$ ppm for DMSO-$d_6$. $^{13}$C-NMR spectra were recorded on the same spectrometer at 100 MHz and referenced to solvent signals $\delta = 77$ ppm for CDCl$_3$ and $\delta 39.50$ ppm for DMSO-$d_6$. DEPT 135 NMR spectroscopy was used where appropriate to aid the assignment of signals in the $^1$H and $^{13}$C-NMR spectra. The mass spectra were recorded on a Shimadzu GCMS-QP-1000 EX mass spectrometer (Kyoto, Japan) at 70 eV using the electron ionization technique. Homogeneity of all compounds synthesized was checked by TLC which was performed on Merck 60 (Munchen, Germany) ready-to-use silica gel plates to monitor the reactions and test the purity of the new synthesized compounds. Compounds 1a–c were prepared by a previously reported method [2].

3.2. General Procedure for the Preparation of Compounds 2a–e

An equimolar mixture of compounds 1a–c (0.01 mol) and the hydrazine derivatives, namely hydrazine hydrate, methyl hydrazine and phenyl hydrazine (0.01 mol) in 50 mL ethanol was refluxed for 6 h. The solid that separated after cooling was filtered off, washed with petroleum ether (b.p 40–60 °C), dried and then crystallized from ethanol.

3-Amino-5,5-di(4-methylphenyl)-1H-pyrazol-4(5H)-one (2a). Yield 73%. m.p. 230–232 °C. IR (KBr), $\nu$ cm$^{-1}$: 3310, 3270 (NH$_2$, NH), 3056 (CH$_{Ar}$), 1713 (CO). $^1$H-NMR (DMSO-$d_6$): $\delta$ at 2.13 (s, 6H, 2CH$_3$), 7.09–7.86 (m, 8H, ArH), 8.83 (bs, 2H, NH$_2$, D$_2$O exchangeable) 11.81 (s, 1H, NH D$_2$O exchangeable), $^{13}$C-NMR (DMSO-$d_6$) $\delta$ ppm: 23.6 (CH$_3$), 75.2 (C5), 130.5, 131.7, 134.3, 135.8, 144.4 (aromatic + C=N), 191.6 (C=O). MS: $m/z$ 279 [M$^+$] (34%). Anal. Calc. for C$_{17}$H$_{17}$N$_3$O (279): C, 73.11; H, 6.09; N 15.05; found: C, 73.39; H, 5.87; N, 15.44.

3-Amino-5,5-di(4-methoxyphenyl)-1H-pyrazol-4(5H)-one (2b). Yield 77%. m.p. 246–248 °C. IR (KBr), $\nu$ cm$^{-1}$: 3436, 3276 (NH$_2$, NH), 3063 (CH$_{Ar}$), 1712 (CO). $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.53 (s, 6H, 2OCH$_3$), 7.43–7.82 (m, 8H, ArH), 12.12 (bs, 2H, NH$_2$, D$_2$O exchangeable), and 13.24 (bs, 1H, NH, D$_2$O exchangeable). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ ppm: 59.8 (CH$_3$), 77.1 (C5), 116.7, 128.4, 134.6, 143.8, 153.5 (aromatic + C=N), 191.1 (C=O). MS: $m/z$ 311 [M$^+$] (23.7%). Anal. Calc. for C$_{17}$H$_{17}$N$_3$O$_3$ (311): C, 65.59; H, 5.46; N, 15.43. found: C, 65.23, H, 5.31, N 15.05.

3-Amino-5,5-di(4-nitrophenyl)-1H-pyrazol-4(5H)-one (2c). Yield 65%. m.p. 182–184 °C. IR (KBr), $\nu$ cm$^{-1}$: 3457, 3338 (NH$_2$, NH), 3065 (CH$_{Ar}$), 1718 (CO). $^1$H-NMR(DMSO-$d_6$): $\delta$ 7.32–7.82 (m, 8H, ArH), 11.86 (bs, 2H, NH$_2$, D$_2$O exchangeable) and 12.85 (bs, 1H, NH, D$_2$O exchangeable). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ ppm: 59.8 (CH$_3$), 77.1 (C5), 116.7, 128.4, 134.6, 143.8, 153.5 (aromatic + C=N), 191.1 (C=O). MS: $m/z$ 341 [M$^+$] (14.8%). Anal. Calc. for C$_{15}$H$_{11}$N$_5$O$_5$ (341): C, 52.78; H, 3.22; N, 20.53; found: C, 53.02; H, 3.08, N, 20.89.

3-Amino-5,5-di(4-methylphenyl)-1-methyl-pyrazol-4(5H)-one (2d). Yield 64%. m.p. 204–206 °C. IR (KBr), $\nu$ cm$^{-1}$: 3234 (NH$_2$, NH), 3056 (CH$_{Ar}$), 1722 (CO). $^1$H-NMR(DMSO-$d_6$): $\delta$ 2.21 (s, 6H, 2CH$_3$Ar), 3.36 (s, 3H, CH$_3$), 7.21–7.66 (m, 8H, ArH), 11.27 (bs, 2H, NH$_2$, D$_2$O exchangeable). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ ppm: 22.7 (CH$_3$), 38.5 (CH$_3$), 78.6 (C5), 130.6, 132.3, 133.5, 137.9, 144.1 (aromatic + C=N), 192.0 (C=O). MS: $m/z$ 293 [M$^+$] (12.9%). Anal. Calc. for C$_{18}$H$_{19}$N$_3$O (293): C, 73.72; H, 6. 48; N, 14.33; found: C, 74.00; H, 6.75; N, 14.00.
3-Amino-5,5-di(4-methylphenyl)-1-phenyl-pyrazol-4(5H)-one (2e). Yield 60%. m.p. 218–220 °C. IR (KBr), ν cm\(^{-1}\): 3321 (NH\(_2\)), 3060 (CH\(_{Ar}\)), 1720 (CO). \(^1\)HNMR (DMSO-\(d_6\)): δ 2.26 (s, 6H, 2CH\(_3\)), multiplet at 7.28–7.80 (m, 13H, ArH), 10.17 (bs, 2H, NH\(_2\), D\(_2\)O exchangeable). \(^1\)C-NMR (DMSO-\(d_6\)) δ ppm: 23.1 (CH\(_3\)), 76.7 (C5), 117.8, 123.6, 126.8, 130.8, 132.1, 133.1, 135.5, 141.7, 144.6 (aromatic + C=\(\equiv\)N), 192.6 (C=O). MS: m/z 355 [M\(^+\)] (8.9%). Anal. Calc. for C\(_{23}\)H\(_{21}\)N\(_3\)O (355): C, 77.74; H, 5.91; N, 11.83; found: C, 78.05; H, 5.77; N, 11.50.

3.3. General Procedure for the Preparation of the Compounds 3a–c

A mixture of 1a–c (0.01 mol) and hydroxylamine hydrochloride (1.03 g; 0.015 mol) in boiling pyridine (50 mL) was heated under reflux for 5h. The reaction mixture was allowed to cool, poured into ice/HCl. The product that precipitated was filtered, dried, and recrystallized from dioxane.

3-Amino-5,5-di(4-methylphenyl)-isoxazol-4(5H)-one (3a). Yield 73%. m.p. 222–224 °C. IR (KBr), ν cm\(^{-1}\): 3357 (NH\(_2\)), 3056 (CH\(_{Ar}\)), 1706 (CO). \(^1\)H-NMR (DMSO-\(d_6\)): δ 2.11 (s, 6H, 2CH\(_3\)), 7.25–7.80 (m, 8H, Ar-H), 8.11 (bs, 2H, NH\(_2\), D\(_2\)O exchangeable). \(^1\)C-NMR (DMSO-\(d_6\)) δ ppm: 23.4 (CH\(_3\)), 101.7 (C5), 128.3, 130.4, 134.6, 140.0, 149.2 (aromatic + C=\(\equiv\)N), 193.0 (C=O). MS: m/z 280 [M\(^+\)] (4.6%). Anal. Calc. for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_2\) (280): C, 72.86; H, 5.71; N, 10.00; found: C, 72.57; H, 5.55; N, 10.32.

3-Amino-5,5-di(4-methoxyphenyl)-isoxazol-4(5H)-one (3b). Yield 77%. m.p. 250–252 °C. IR (KBr), ν cm\(^{-1}\): 3299 (NH\(_2\)), 3054 (CH\(_{Ar}\)), 1724 (CO). \(^1\)H-NMR (DMSO-\(d_6\)): δ 3.67 (s, 6H, 2OCH\(_3\)), 7.23–7.89 (m, 8H, Ar-H), 9.21 (bs, 2H, NH\(_2\), D\(_2\)O exchangeable). \(^1\)C-NMR (DMSO-\(d_6\)) δ ppm: 58.2 (CH\(_3\)), 102.2 (C5), 120.6, 129.1, 135.2, 149.5, 154.4 (aromatic + C=\(\equiv\)N), 192.1 (C=O). MS: m/z 312 [M\(^+\)] (15.7%). Anal. Calc. for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_4\) (312): C, 65.38; H, 5.13; N, 8.97; found: C, 65.00; H, 4.99; N, 8.65.

3-Amino-5,5-di(4-nitrophenyl)-isoxazol-4(5H)-one (3c). Yield 68%. m.p. 204–206 °C. IR (KBr), ν cm\(^{-1}\): 3448 (NH\(_2\)), 3058 (CH\(_{Ar}\)), 1723 (CO). \(^1\)H-NMR (DMSO-\(d_6\)): δ 7.16–7.74 (m, 8H, Ar-H), 8.78 (bs, 2H, NH\(_2\), D\(_2\)O exchangeable). MS: m/z 342 [M\(^+\)] (12.8%). Anal. Calc. for C\(_{15}\)H\(_{10}\)N\(_4\)O\(_6\) (342): C, 52.63; H, 2.92; N, 16.37; found: C, 52.99; H, 2.80; N, 16.05.

3.4. 6-Amino-7-hydroxy-7,7a-di(4-methylphenyl)-7,7a-dihydro-1H-pyrrolo[2,3-e][1,2,4]-triazine-3(2H)-thione (4)

An equimolar mixture of compound 1a (2.74 g; 0.01 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in 50 mL ethanol was refluxed for 4 h. The solid that separated after cooling was filtered off, dried and then, recrystallized from ethanol. Yield 70%. m.p. 192–194 °C. IR (KBr), ν cm\(^{-1}\): 3543 (OH), 3408 (NH\(_2\)), 3287, 3209 (NH), 3052 (CH\(_{Ar}\)), 2860 (SH), 1629 (C=\(\equiv\)N). \(^1\)H-NMR (DMSO-\(d_6\)): δ 7.16–7.74 (m, 8H, Ar-H), 8.78 (bs, 2H, NH\(_2\), D\(_2\)O exchangeable) 12.07, 12.52 (bs, 2H, NH\(_2\), D\(_2\)O exchangeable). C-NMR (DMSO-\(d_6\)) δ ppm: 23.1 (CH\(_3\)), 66.9, 92.4 (saturated-C), 124.7, 125.4, 126.4, 127.8, 135.3, 136.1, 140.1, 145.3, 157.2, 158.3 (Aromatic + C=\(\equiv\)N), 179.9 (C=\(\equiv\)S). MS: m/z 365 [M\(^+\)] (21.4%). Anal. Calc. for C\(_{19}\)H\(_{19}\)N\(_5\)O\(_3\) (365): C, 62.47; H, 5.20; N, 19.18, S, 8.77; found: C, 62.18, H, 5.40, N, 18.87, S, 8.45.
3.5. (6-(4-Methylbenzoyl)-2-phenyl-6-(4-methyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5(6H)-one (5)

A mixture of 1a (2.74g, 0.01 mol) and 2-amino-5-phenyl-1,3,4-thiadiazole (1.77 g; 0.01 mol) in ethanol (50 mL) was refluxed for 4h, then left to cool. The separated solid product was filtered off, dried and recrystallized from toluene-ethanol mixture. Yield 65%. m.p. 152–154 °C. IR (KBr), νcm⁻¹: 3052 (CHAr), 1668, 1687 (CO), 1613 (C=N). ¹H-NMR (DMSO-d₆): δ 2.14 (s, 3H, CH₃), 7.24–7.81 (m, 13H, ArH). ¹³C-NMR (DMSO-d₆) δ ppm: 22.4 (CH₃), 84.4 (saturated-C), 127.3, 128.1, 129.6, 130.4, 131.7, 132.6, 133.4, 134. 3, 135.2, 136.3, 137.5, 138.2, 141.7, 146.9, 149.3 (aromatic + C=N), 175.8, 199.1, (C=O). MS: m/z 425 [M⁺] (5.1%). Anal. Calc. for C25H19N3O2S (425): C, 70.59; H, 4.47; N, 9.88; S, 7.53; found: C, 70.95; H, 4.28; N, 9.52; S, 7.80.

3.6. General Procedure for the Preparation of Compounds 6a–c

An equimolar mixture of compounds 1a–c (0.01 mol) and hydrazine hydrate (0.5 mL, 0.01 mol) in n-butanol (30 mL) was refluxed for 8 h. The solid that separated after cooling was filtered off, washed by petroleum ether (b.p. 40–60 °C), dried and then crystallized from n-butanol to afford compounds 7a–c. The mother liquor (n-butanol) was evaporated under vacuum till dryness. The obtained solid was crystallized from ethanol producing compounds 2a–c.

2,2,6,6-Tetra(4-methylphenyl)-5,6-dihydro-2H-pyrazolo[1,5-a]imidazole-3,7-dione (6a). Yield 30%. m.p. 296–298 °C. IR (KBr), ν cm⁻¹: 3119 (NH), 3074 (CHAr), 1669, 1652 (C=O). ¹H-NMR (DMSO-d₆): δ 2.14, 2.36 (s, 12H, 4CH₃), 7.04–7.58 (m, 16H, ArH), 12.33 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 22.4 (CH₃), 79.9, 87.8 (saturated-C), 130.3, 131.4, 134.8, 137.1, 138.2, 140.1, 140.9, 148.8 (aromatic + C=N), 177.8, 184.5, 190.8 (C=O). MS: m/z 499 [M⁺] (7.75). Anal. Calc. for C33H29N3O2 (499): C, 79.36; H, 5.81; N, 7.42; found: C, 79.36; H, 5.81; N, 7.42.

2,2,6,6-Tetra(4-methoxyphenyl)-5,6-dihydro-2H-pyrazolo[1,5-a]imidazole-3,7-dione (6b). Yield 27%. m.p. 282–284 °C. IR (KBr), ν cm⁻¹: 3331 (NH), 3050 (CHAr), 1680, 1666 (C=O). ¹H-NMR (DMSO-d₆): δ 3.72, 3.86 (s, 12H, 4OCH₃), 7.54–8.20 (m, 16H, ArH), 12.51 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 57.1 (CH₃), 78.8, 88.1 (saturated-C), 118.7, 130.5, 133.2, 134.1, 146.3, 149.9 (aromatic + C=N), 177.8, 194.4 (C=O). MS: m/z 563 [M⁺] (13.4%). Anal. Calc. for C33H29N3O6 (563): C, 70.36; H, 5.81; N, 7.42; found: C, 70.36; H, 5.81; N, 7.42.

2,2,6,6-Tetra(4-nitrophenyl)-5,6-dihydro-2H-pyrazolo[1,5-a]imidazole-3,7-dione (6c). Yield 25%. m.p. 260–262 °C. IR (KBr), ν cm⁻¹: 3276 (NH), 3073(CHAr), 1685, 1669 (C=O). ¹H-NMR (DMSO-d₆): δ 7.37–7.94 (m, 16H, ArH), 12.89 (bs, 1H, NH, D₂O exchangeable). MS: m/z 623 [M⁺] (44.4%). Anal. Calc. for C29H17N7O10 (623): C, 55.85; H, 2.72; N, 15.73; found: C, 55.84; H, 2.70; N, 15.70.

3.7. General Procedure for the Preparation of the Schiff’s Bases 7a–d

A mixture of compounds 2a–c (0.01 mol) and aromatic aldehyde, namely benzaldehyde and/or p-chlorobenzaldehyde (0.01 mol) in ethanol (50 mL) was refluxed for 4 h. The solid that separated after cooling was filtered off, dried and then crystallized from ethanol.
3-(Benzylideneamino)-5,5-di(4-methylphenyl)-1H-pyrazol-4(5H)-one (7a). Yield 70%. m.p. 212–214 °C. IR (KBr), ν cm⁻¹: 3221 (NH), 3056 (CH₂), 1676 (CO). ¹H-NMR (DMSO-d₆): δ 2.25 (s, 6H, 2CH₃), 6.22 (s, 1H, CH=), 7.19–7.92 (m, 13H, ArH), 11.24 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 23.3 (CH₃), 75.7 (saturated-C), 127.4, 128.6, 130.2, 131.4, 133.9, 134.7, 135.6, 137.9, 147.1, 152.6 (aromatic + C=N), 191.5 (C=O). MS: m/z 367 [M⁺]. 274, 194, 176, 145. Anal. Calc. for C₂₄H₂₁N₃O (367): C, 78.47; H, 5.72; N, 11.44; found: C, 78.81; H, 5.55; N, 11.12.

3-(Benzylideneamino)-5,5-di(4-methoxyphenyl)-1H-pyrazol-4(5H)-one (7b). Yield 75%. m.p. 226–228 °C. IR (KBr), ν cm⁻¹: 3211 (NH), 3058 (CH Ar), 1670 (CO). ¹H-NMR (DMSO-d₆): δ 3.71 (s, 6H, 2OCH₃), 6.31 (s, 1H, CH=), 7.16–7.97 (m, 13H, ArH), 11.32 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 59.3 (CH₃), 77.4 (saturated-C), 116.2, 128.6, 130.1, 131.5, 133.2, 134.6, 135.8, 148.5, 149.8, 153.5 (aromatic + C=N), 189.5 (C=O). MS: m/z 399 [M⁺] (28.2%). Anal. Calc. for C₂₄H₂₁N₃O₃ (399): C, 72.18; H, 5.26; N, 10.53; found: C, 71.83; H, 5.61; N, 10.35.

3-(Benzylideneamino)-5,5-di(4-nitrophenyl)-1H-pyrazol-4(5H)-one (7c). Yield 65%. m.p. 210–212 °C. IR (KBr), ν cm⁻¹: 3278 (NH), 3080 (CH Ar), 1680 (CO). ¹H-NMR (DMSO-d₆): δ 6.47 (s, 1H, CH=), 7.14–8.00 (m, 13H, ArH), 10.11 (bs, 1H, NH, D₂O exchangeable). MS: m/z 429 [M⁺] (25.6%). Anal. Calc. for C₂₂H₁₅N₅O₅ (429): C, 67.71; H, 4.07; N, 13.16; found: C, 67.70; H, 4.02; N, 13.15.

3-(4-Chlorobenzylidinimino)-5,5-di(4-methylphenyl)-1H-pyrazol-4(5H)-one (7d). Yield 72%. m.p. 226–228 °C. IR (KBr), ν cm⁻¹: 3290 (NH), 3052 (CH₂), 1672 (CO). ¹H-NMR (DMSO-d₆): δ 2.28 (s, 6H, 2CH₃), 6.57 (s, 1H, CH=), 7.31–7.95 (m, 12H, ArH), 11.00 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 23.0 (CH₃), 75.1 (saturated-C), 127.7, 128.8, 130.0, 131.6, 133.5, 134.8, 135.8, 137.5, 147.4, 153.1 (aromatic + C=N), 178.4 (C=O). MS: m/z 401 [M⁺] (33.6%), [M + 2] (11.1%). Anal. Calc. for C₂₄H₂₀N₃OCl (401.5): C, 71.73; H, 4.98; N, 10.46; Cl, 8.84; found: C, 70.65; H, 4.26; N, 11.21; Cl, 8.51.

3.8. 3,3-Di(4-methylphenyl)-2,3-dihydro-1H-pyrazolo[4,3-b]pyrazin-6(7H)-one (8)

A mixture of compound 2a (2.76 g; 0.01 mol) and methyl glycinate (1 mL, 0.01 mol) in ethanol (50 mL) was refluxed for 4 h. The solid that separated out after cooling was filtered off, dried and then recrystallized from dioxane. Yield 70%. m.p. 164–166 °C. IR (KBr), ν cm⁻¹: 3277–3226 (NH), 3050 (CH₂), 1668 (C=O). ¹H-NMR (DMSO-d₆): δ 2.20 (s, 6H, 2CH₃), 6.77 (s, 1H, CHpy), 7.21–7.80 (m, 8H, ArH), 6.4, 9.7 and 12.4 (3bs, 3H, 3NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 23.0 (CH₃), 75.9 (saturated-C), 115.8, 130.1, 131.5, 134.0, 137.4, 138.7, 142.6 (aromatic + C=N), 178.4 (C=O). MS: m/z 318 [M⁺] (23.9%). Anal. Calc. for C₁₉H₁₈N₃O (318): C, 71.70; H, 5.66; N, 17.61; found: C, 71.47; H, 5.48; N, 17.28.

3.9. General Procedure for the Preparation of the Compounds 9a–c

A mixture of compounds 7a–c (0.01 mol) and ammonium acetate (2.31 g, 0.03 mol) was heated in an oil bath at 90 °C for 3 h. The mixture was left to cool then washed with water several times. The solid product was filtered off, dried and then, crystallized from dioxane.
3,3-Di(4-methylphenyl)-5-phenyl-4,5-dihydroimidazo[4,5-c]pyrazole (9a). Yield 69%. m.p. 164–166 °C. IR (KBr), ν cm⁻¹: 3233, 3196 (NH), 3066 (CH Ar), 1604 (C=N). ¹H-NMR (DMSO-d₆): δ 2.26 (s, 6H, 2CH₃), 5.13 (s, 1H, imidazol), 7.23–7.73 (m, 13H, ArH), 9.71 and 10.49 (bs, 2H, 2NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 22.9 (CH₃), 67.1, 75.8 (saturated-C), 117.6, 124.5, 127.8, 128.7, 130.4, 131.9, 133.8, 137.7, 141.4, 143.3 (aromatic-C). MS: m/z 366 [M⁺] (55.1%). Anal. Calc. for C₂₄H₂₂N₄ (366): C, 78.69; H, 6.01; N, 15.30; found: C, 78.96; H, 5.75; N, 15.62.

3,3-Di(4-methoxyphenyl)-5-phenyl-4,5-dihydroimidazo[4,5-c]pyrazole (9b). Yield 74%. m.p. 180–182 °C. IR (KBr), ν cm⁻¹: 3280, 3208 (NH), 3050 (CH Ar), 1614 (C=N). ¹H-NMR (DMSO-d₆): δ 3.85 (s, 6H, 2CH₃), 5.28 (s, 1H, imidazol), 7.12–7.92 (m, 13H, ArH), 8.88 and 9.99 (bs, 2H, 2NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 58.7 (CH₃), 67.4, 75.2 (saturated-C), 118.5, 124.8, 127.2, 128.9, 130.7, 131.7, 133.5, 136.7, 145.8, 149.6 (aromatic-C). MS: m/z 398 [M⁺] (43.8%). Anal. Calc. for C₂₄H₂₂N₄O₂ (398): C, 72.36; H, 5.53; N, 14.07; found: C, 71.98; H, 5.75; N, 13.76.

3,3-Di(4-nitrophenyl)-5-phenyl-4,5-dihydroimidazo[4,5-c]pyrazole (9c). Yield 66%. m.p. 224–228 °C. IR (KBr), ν cm⁻¹: 3278, 3202 (NH), 3080 (CH Ar), 1629 (C=N). ¹H-NMR (DMSO-d₆): δ 5.41 (s, 1H, imidazol), 7.34–8.23 (m, 13H, ArH), 10.22 and 11.09 (bs, 3H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 66.8, 75.2 (saturated-C) 120.8, 124.2, 126.1, 127.8, 129.5, 130.6, 131.7, 142.5, 146.3, 147.8 (aromatic-C). MS: m/z 428 [M⁺] (48.2%). Anal. Calc. for C₂₂H₁₆N₆O₄ (428): C, 61.68; H, 3.74; N, 19.63; found: C, 61.89; H, 4.01; N, 19.99.

3.10. General Procedure for the Preparation of the Compounds 10a–c

An equimolar mixture of compounds 7a–c (0.01 mol) and hydrazine hydrate (0.5 mL, 0.01 mol) in ethanol (50 mL) was refluxed for 6 h. The solid that separated out after cooling was filtered off, washed with petroleum ether (b.p. 40–60 °C), dried and then crystallized from ethanol.

7,7-Di(4-methylphenyl)-3-phenyl-2,3,4,7-tetrahydro-1H-pyrazolo[3,4-e][1,2,4]triazine (10a). Yield 70%. m.p. 190–192 °C. IR (KBr), ν cm⁻¹: 3298, 3260, 3182 (NH), 3063 (CH Ar), 1630 (C=N). ¹H-NMR (DMSO-d₆): δ 2.22 (s, 6H, 2CH₃), 5.55 (s, 1H, triazine), 7.13–7.88 (m, 13H, ArH), 9.13, 10.27 and 11.07 (bs, 3H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 70.2, 76.4 (saturated-C), 118.2, 124.8, 127.4, 128.9, 130.5, 131.7, 133.5, 137.2, 142.1, 145.1 (aromatic-C). MS: m/z 381 [M⁺] (22.3%). Anal. Calc. for C₂₄H₂₃N₅ (381): C, 75.59; H, 6.04; N, 18.37; found: C, 75.75; H, 5.86; N, 18.02.

7,7-Di(4-methoxyphenyl)-3-phenyl-2,3,4,7-tetrahydro-1H-pyrazolo[3,4-e][1,2,4]triazine (10b). Yield 72%. m.p. 181–183 °C. IR (KBr), ν cm⁻¹: 3284, 3222, 3200 (NH), 3056 (CH Ar), 1641 (C=N). ¹H-NMR (DMSO-d₆): δ 3.79 (s, 6H, 2OCH₃), 5.42 (s, 1H, triazine), 7.30–7.79 (m, 13H, ArH), 9.38, 10.30 and 12.00 (bs, 3H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 59.1 (CH₃), 70.8, 77.3 (saturated-C), 111.7, 124.1, 126.8, 128.6, 129.9, 131.4, 133.8, 137.1, 146.2, 150.5 (aromatic-C). MS: m/z 413 [M⁺] (26.1%). Anal. Calc. for C₂₄H₂₃N₅O₂ (413): C, 69.73; H, 5.57; N, 16.95; found: C, 70.01; H, 5.71; N, 16.60.

7,7-Di(4-nitrophenyl)-3-phenyl-2,3,4,7-tetrahydro-1H-pyrazolo[3,4-e][1,2,4]triazine (10c). Yield 68%.
m.p. 241–243 °C. IR (KBr), ν cm⁻¹: ν 3300, 3268, 3190 (NH), 3080 (CH Ar), 1632 (C=N). ¹H-NMR (DMSO-ᵈₑ): δ 4.8 (s, 1H, triazine), 7.31–8.28 (m, 13H, ArH), 8.49, 10.01 and 11.77 (bs, 3H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-ᵈₑ) δ ppm: 69.9, 75.9 (saturated-C) 116.4, 121.4, 126.5, 127.6, 129.7, 130.7, 132.1, 138.0, 146.0, 149.9 (aromatic-C). MS: m/z 443 [M⁺] (27.7%). Anal. Calc. for C₂₂H₁₇N₇O₄ (443): C, 59.59; H, 3.84; N, 22.12; found: C, 59.85; H, 4.07; N, 21.77.

3.11. 4,4-Di(4-methylphenyl)-3,4-dihydro-7H-2a,3,5,7a-tetraazacyclopenta[c,d]indene-1,7-(2H)-dione (11).

An equimolar mixture of compound 8 (3.18 g; 0.01 mol) and chloroacetic acid (1 g; 0.01 mol) in phosphorous oxychloride (20 mL) was refluxed for 2 h. After cooling, the reaction mixture was poured onto ice/H₂O, the solid that separated out was filtered off, washed with petroleum ether (b.p. 40–60 °C), dried and then crystallized from toluene. Yield 55%. m.p. 170–172 °C. IR (KBr), ν cm⁻¹: 3222 (NH), 1677, 1657 (CO), 1613 (C=N). ¹H-NMR (DMSO-ᵈₑ): δ 2.16 (s, 6H, 2CH₃), 4.17 (s, 2H, CH₂), 6.72 (s, 1H, pyrazine), 7.44–7.76 (m, 8H, ArH), 8.72 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-ᵈₑ) δ ppm: 23.2 (CH₃), 57.1, 76.8 (sp³-C), 117.4, 127.8, 130.7, 131.9, 134.1, 137.6, 145.1 (aromatic + sp²-C), 160.2, 170.1 (C=O). MS: m/z 358 [M⁺] (43.7%). Anal. Calc. for C₂₁H₁₈N₄O₂ (358): C, 70.39; H, 5.03; N, 15.64; found: C, 70.08; H, 4.81; N, 16.01.

3.12. 10,10-Di(4-methylphenyl)-4,10-dihydro-3H,6H-pyrazolo[1',2':1,2]pyrazolo[3,4-b]-pyrazine-3,6,8-(7H)-trione (12).

A mixture of compound 8 (3.18 g; 0.01 mol) and diethyl malonate (2.4 mL; 0.015 mol) in ethanol (50 mL) was refluxed for 4 h. The solid that separated out after cooling was filtered off, washed with petroleum ether (b.p. 40–60 °C), dried and then recrystallized from ethanol. Yield 57%. m.p. 224–226 °C. IR (KBr), ν cm⁻¹: 3245 (NH), 1691, 1672, 1659 (CO), 1620 (C=N). ¹H-NMR (DMSO-ᵈₑ): δ 2.15 (s, 6H, 2CH₃), 4.51 (s, 2H, COCH₂CO), 6.81 (s, 1H, pyrazine), 7.32–7.83 (s, 8H, ArH), 10.14 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-ᵈₑ) δ ppm: 23.0 (CH₃), 49.4, 76.0 (saturated-C), 117.0, 127.4, 130.0, 131.2, 134.7, 138.0, 145.9 (aromatic + C=N), 161.3, 170.9, 175.3 (C=O). MS: m/z 386 [M⁺] (44.4%). Anal. Calc. for C₂₂H₁₈N₄O₃ (386): C, 68.39; H, 4.66; N, 14.51; found: C, 68.07; H, 4.88; N, 14.22.

3.13. 7-Benzylidene-10,10-di(4-methylphenyl)-4,10-dihydro-3H,6H-pyrazolo[1',2':1,2]pyrazolo[3,4-b]-pyrazine-3,6,8-(7H)-trione (13).

An equimolar mixture of compound 12 (3.86 g; 0.01 mol) and benzaldehyde (1.06 mL; 0.01 mol) in ethanol (50 mL) was refluxed for 6 h. The solid that separated after cooling was filtered off, dried and then crystallized from n-butanol. Yield 24%. m.p. 266–268 °C. IR (KBr), ν cm⁻¹: 3290 (NH), 1687, 1677, 1666, (CO), 1626 (C=N). ¹H-NMR (DMSO-ᵈₑ): δ 2.26 (s, 6H, 2CH₃), 6.44, 6.87 (bs, 2H, benzylic and pyrazine), 7.27–7.87 (m, 13H, ArH), 9.82 (bs, 1H, NH, D₂O exchangeable). ¹³C-NMR (DMSO-ᵈₑ) δ ppm: 23.4 (CH₃), 76.5 (saturated-C), 117.8, 125.1, 126.4, 127.7, 128.9, 130.0, 131.2, 133.0, 134.7, 136.3, 138.0, 145.9, 150.7 (aromatic + C=N), 160.5, 171.2, 173.7 (C=O). MS: m/z 474 [M⁺] (77.6%). Anal. Calc. for C₂₉H₂₂N₄O₃ (474): C, 73.42; H, 4.64; N, 11.81; found: C 73.05; H, 4.35; N, 12.13.
3.14. General Procedure for the Preparation of Compounds 14a,b

An equimolar mixture of compound 1a (2.74 g; 0.01 mol) and an active methylene precursor, e.g., acetylacetone and/or cyclopentanone (0.01 mol) and aqueous NaOH (50%, 8 mL) in ethanol (50 mL) was refluxed for 3 h and left overnight. The reaction mixture was poured into ice/HCl. The solid so formed filtered off, washed with water, dried and then crystallized from ethanol.

3,3-Diacetyl-1,2-di(4-methylphenyl)-1,2-dicyanopropanol (14a). Yield 70%. m.p. 220–222 °C. IR (KBr), ν cm⁻¹: 3380 (OH), 3062 (CHAr), 2240, 2220 (CN), 1688 (CO). ¹H-NMR (DMSO-d₆): δ 2.19 (s, 6H, 2CH₃), 2.43 (s, 6H, 2CH₃), 4.29 (s, 1H, COCHCO), 5.55 (bs, 1H, OH, D₂O exchangeable), 7.25–7.84 (m, 8H, ArH). ¹³C-NMR (DMSO-d₆) δ ppm: 22.5, 30.2, 36.0, 63.1, 78.2 (saturated-C), 116.8, 120.0 (CN), 125.3, 127.1, 129.6, 131.2, 134.6, 136.8, 141.1, 146.9 (aromatic-C), 200.2 (C=O). MS: m/z 374 [M⁺] (87.4%). Anal. Calc. for C₂₃H₂₂N₂O₃ (374): C, 73.80; H, 5.88; N, 7.48; found: C, 74.15; H, 5.67; N, 7.16.

1,2-Dicyano-1,2-di(4-methylphenyl)-2-(2-oxocyclopentyl)ethanol (14b). Yield 67%. m.p. 192–194 °C. IR (KBr), ν cm⁻¹: 3367 (OH), 3051 (CHAr), 2950 (CHAli), 2243, 2221 (CN), 1677 (CO), ¹H-NMR (DMSO-d₆): δ 1.79–2.01 (m, 6H, CHcyclopent.), 2.13 (s, 6H, 2CH₃), 2.31 (s, 1H, CHcyclopent), 5.88 (bs, 1H, OH, D₂O exchangeable), 7.15–7.78 (m, 8H, ArH). ¹³C-NMR (DMSO-d₆) δ ppm: 15.4, 21.5, 22.7, 36.9, 42.3, 52.0, 77.2 (saturated-C), 116.1, 119.2 (CN), 125.5, 127.4, 129.9, 130.9, 133.8, 136.3, 141.1, 145.2 (aromatic-C), 209.0 (C=O). MS: m/z 358 [M⁺] (77.7%). Anal. Calc. for C₂₃H₂₂N₂O₂ (358): C, 76.09; H, 6.15; N, 8.14.

3.15. General Procedure for the Preparation of the Compounds 15a,b

Compounds 14a,b (0.01 mol) and ammonium acetate (2.31 g, 0.03 mol) were mixed thoroughly and fused in an oil bath at 150 °C for 2 h. Left to cool, then washed with water several times. The solid product was dried and recrystallized from benzene.

5-Acetyl-2-amino-6-methyl-4,4-di(4-methylpheny)pyridin-3(4H)-one (15a). Yield 74%. m.p. 210–212 °C. IR (KBr), ν cm⁻¹: 3285 (NH₂). 1691, 1665 (CO), 1630 (C=N), ¹H-NMR (DMSO-d₆): δ 2.14 (s, 6H, 2CH₃), 2.41 (s, 3H, CH₃), 2.77 (s, 3H, CH₃), 7.44–7.83 (m, 8H, ArH), 9.42 (bs, 2H, NH₂, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 22.5, 23.6, 28.5 (CH₂-cyclopentane), 78.2 (saturated-C), 128.7, 130.0, 131.9, 133.2, 137.4, 140.9, 145.6 (aromatic + C=N), 192.7, 198.00 (C=O). MS: m/z 346 [M⁺] (41.8%). Anal. Calc. for C₂₂H₂₂N₂O₂ (346): C, 76.30; H, 6.36; N, 8.09; found: C, 76.60; H, 6.00; N, 8.41.

2-Amino-4,4-(4-methylphenyl)-4,5,6,7-tetrahydro-3H-cyclopenta[b]pyridin-3-one (15b). Yield 65%. m.p. 176–178 °C. IR (KBr) ν cm⁻¹: 1613 (C=N), 1685 (CO), 3272 (NH). ¹H-NMR (DMSO-d₆): δ 1.79 (q, 2H, CH₂-cyclopentane), 2.17–2.41 (m, 10H, 2CH₃, 2CH₂-cyclopentane), 7.32–7.73 (m, 8H, ArH), 9.66 (bs, 2H, NH₂, D₂O exchangeable). ¹³C-NMR (DMSO-d₆) δ ppm: 20.8, 22.4, 26.9, 47.1, 54.0 (saturated-C), 129.2, 130.4, 131.6, 133.8, 137.4, 140.9, 141.8 (aromatic + C=N), 192.0 (C=O). MS: m/z 330 [M⁺] (37.6%). Anal. Calc. for C₂₂H₂₂N₂O (330): C, 79.97; H, 6.63; N, 8.48; found: C, 79.97; H, 6.63; N, 8.48.
4. Conclusions

In the present work, a series of some Schiff bases and novel fused heterocyclic derivatives 2–15 were synthesized using 2,3-diaryl oxirane-2,3-dicarbonitriles 1a–c as starting materials. Some of newly synthesized compounds were screened against bacterial and fungal strains and most of the newly synthesized compounds showed high antimicrobial activities. The structures of the new compounds were elucidated using IR, $^1$H-NMR, $^{13}$C-NMR and mass spectroscopy.

Acknowledgments

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group project no. RGP-172.

Author Contributions

The listed authors contributed to this work as described in the following. Mohamed E. Azab gave the concepts of the work, interpreted the results and prepared the manuscript, Sameh A. Rizk, carried out the synthetic work, interpreted the results and prepared the manuscript and Abd El-Galil E. Amr interpreted the results and cooperated in the preparation of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest

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**Sample Availability:** Samples of the compounds are available from the authors.

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