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Short communication

SHORT COMMUNICATION

Synthesis and characterization of selected fused isoxazole and pyrazole derivatives and their antimicrobial activity

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Abstract: New potent antibacterials, fused isoxazole and pyrazole derivatives, were synthesized using 5,5-dimethylcyclohexane-1,3-dione (**1**) and 3-[(4-chlorobenzylidene)amino]-2-thioxoimidazolidin-4-one (**2**) as synthons. Aromatic aldehydes on condensation with **1** and **2** gave 2-arylidene-5,5-dimethylcyclohexane-1,3-dione (**3**) and 5-arylidene-3-[(4-chlorobenzylidene)amino]-2--thioxoimidazolidin-4-one (**4**), respectively. Compounds **3** and **4** were forced to undergo heterocyclization reaction with nucleophilic reagents to give the title compounds. The newly synthesized heterocyles (**5**–**8**) were characterized based on their chemical properties and spectroscopic data, and were found to inhibit *Staphylococcus aureus* and *Corynebacterium diphtheriae.*

Keywords: isoxazole; pyrazole; thiohydantoin; dimedone; antibacterial activity.

INTRODUCTION

Bacteria are becoming resistant to ever more antimicrobial agents. Currently, bacterial resistance is combated by the discovery of new drugs. However, microorganisms are becoming resistant more quickly than new drugs are being found, thus, future research in antimicrobial therapy may focus on finding ways to overcome resistance to antimicrobials, or methods to treat infections with alternative means. Thiohydantoins have been proven to have anticonvulsant activity.[1] Compounds that comprise the hydantoin moiety exhibit pharmacological properties.[2–5] Similarly many natural and synthetic products containing heterocyclic rings, such as isoxazoles[6–8] and pyrazoles,[9] were reported to possess various pharmacological activities. These were attributed to the presence of the N-bridge heterocyclic nuclei of isoxazole[10] and pyrazole,[11] which are described to have herbicide[10] and antibacterial[12] activities.

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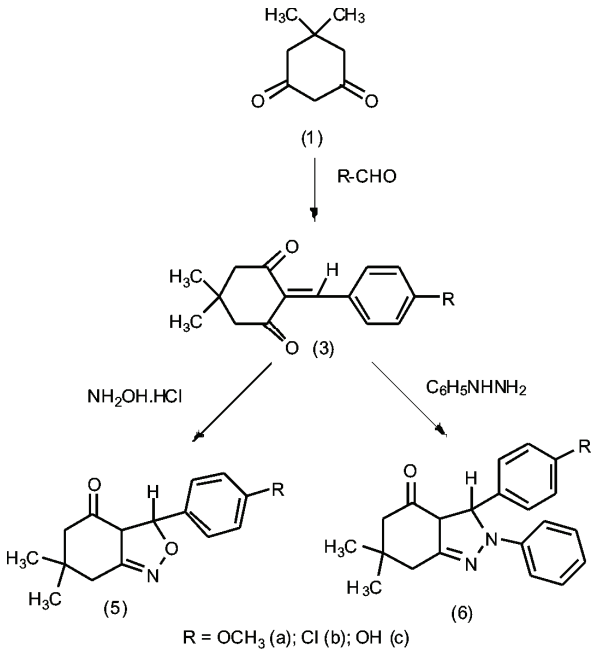
Dimedone and thiohydantoin constitute a unique group of compounds due to the presence of characteristic keto group, which acts as a starting material for more complex compounds. The thiohydantoin/dimedone system possesses reactive sites which can be suitably modified by the introduction of different heterocyclic moieties to yield the potent COX-1/COX-2 inhibitors.[13] Bearing this in mind, twelve new fused compounds containing isoxazole and pyrazole moieties were synthesized in order to act as active pharmaceutical. The structures of synthesized compounds were confirmed by spectral data and elemental analysis.

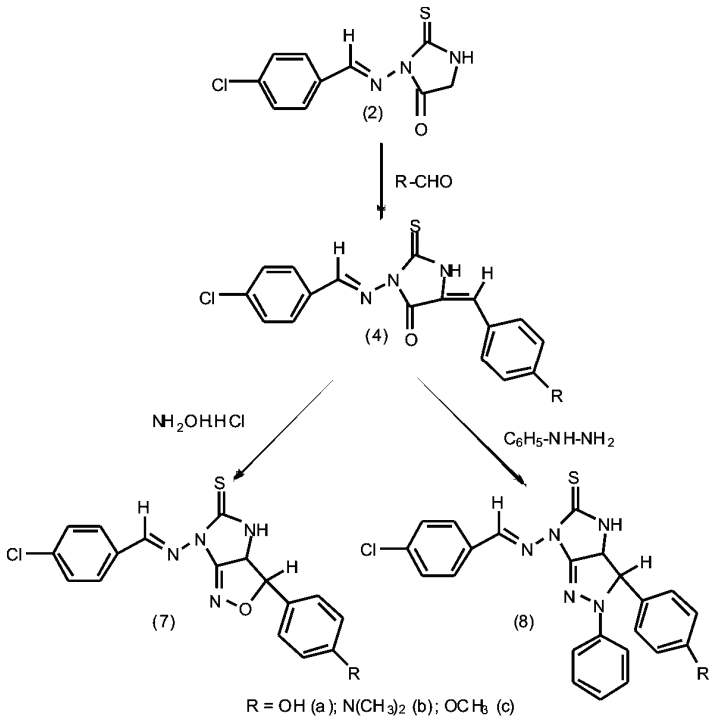
RESULT AND DISCUSSION

Chemistry

The starting material, 5,5-dimethylcyclohexane-1,3-dione (**1**), was obtained by a reported procedure[14] and 3-[(4-chlorobenzylidene)amino]-2-thioxoimidazolidin-4-one (**2**)[15] and derivatives thereof were prepared from the reaction of aromatic aldehydes and thiosemicarbazide to give arylthiosemicarbazone. This was followed by cyclization with ethyl chloroacetate in the presence of fused sodium acetate. Both **1** and **2** (Schemes 1 and 2, respectively) were condensed with appropriate aromatic aldehydes in presence of bases such as piperidine or potassium hydroxide to give 2-arylidene-5,5-dimethylcyclohexane-1,3-dione (**3**) and 5-arylidene-3-[(4-chlorobenzylidene)amino]-2-thioxoimidazolidin-4-one (**4**),[15] respectively. The structures were confirmed based on their chemical and spectral data.



Scheme 1. Reaction pathway for the preparation of compounds **5** and **6.**



Scheme 2. Reaction pathway for the preparation of compounds **7** and **8**.

Cyclocondensation of **3** and **4** with hydroxylamine hydrochloride in the presence of glacial acetic acid yielded 6,6-dimethyl-3-(substitutedphenyl)-3,3a,6,7- -tetrahydro-5*H*-2,1-benz-isoxazol-4-one (**5**) and 6- [(4-chlorobenzylidene)amino-3-(substitutedphenyl)-3a,4-dihydro-3*H*,6*H*-imidazo[4,5-*c*]isoxazole-5-thione (**7**), respectively. Their IR spectra exhibited a band corresponding to –C–O–N (1230 cm^{-1}), which confirmed the presence of the isoxazole ring. The appearance of a peak due to C=N and disappearance of the peak due to C=O in the ^{13}C-NMR spectra further supported the formation of isoxazole.

Compounds **3** and **4** on treatment with phenylhydrazine were transformed into a 3-(substitutedphenyl)-6,6-dimethyl-2-phenyl-2,3,3a,5,6,7-hexahydro-4*H*-indazol-4-one (**6**),[16–18] and 6-[(4-chlorobenzylidine)amino]-2-phenyl-3-(substitutedphenyl)-2,3,3a,4-tetrahydro-6H-imidazo[4,5-*c*]pyrazole5-thione (**8**), in an appreciable yield using potassium hydroxide. Their IR spectra exhibited a band at (1490 cm^{-1}) of N–N and an increased area under the peak in aromatic region, as compared to **3**/**4**, confirms the formation of **6**/**8**. This was also supported by ^{13}C--NMR spectrum, as it revealed a peak of C=N and the disappearance of a peak of C=O. The structures assigned to the compounds were supported by the IR, ^{1}H--NMR, ^{13}C-NMR and mass spectral data and elemental analysis, the results of which are given below.

*2-(4-Methoxybenzylidene)-5,5-dimethylcyclohexane-1,3-dione (**3a**)*. Yield: 62 %; m.p. 130 °C. Anal. Calcd. for $C_{16}H_{18}O_3$ (FW 258.25): C, 74.41; H, 6.97 %. Found: C, 74.32; H, 7.12 %. IR (KBr, cm^{-1}): 1670 (C=O), 1472 (C=C). ^{1}H-NMR ($CDCl_3$, δ / ppm): 0.98 (6H, *s*, 2×CH_3), 2.46 (4H, *s*, 2×CH_2), 3.92 (3H, *s*, OCH_3), 6.99–7.24 (5H, *m*, ArH and C–H). ^{13}C-NMR: 27.32 (2×CH_3), 31.38 (2×CH_2), 40.23 (OCH_3), 115.283, 128–142.64 (C=C and ArC), 162.42 (2×C=O).

*2-(4'-Chlorobenzylidene)-5,5-dimethylcyclohexane-1,3-dione (**3b**)*. Yield: 60 %; m.p. 116 °C. Anal. Calcd. for $C_{15}H_{15}O_2Cl$ (FW 262.66): C, 68.57; H, 5.71 %. Found: C, 68.32; H, 5.89 %. IR (KBr, cm^{-1}): 1665 (C=O), 1498 (C=C), 627 (C–Cl). ^{1}H-NMR ($CDCl_3$, δ / ppm): 0.98 (6H, *s*, 2×CH_3), 2.46 (4H, *s*, 2×CH_2), 7.00––7.24 (5H, *m*, ArH and C–H). ^{13}C-NMR: 27.68 (2×CH_3), 31.65 (2×CH_2), 113.28, 129.5–143.25 (C=C and ArC), 164.56 (2×C=O).

*2-(4-Hydroxybenzylidene)-5,5-dimethylcyclohexane-1,3-dione (**3c**)*. Yield: 57 %; m.p. 122 °C. Anal. Calcd. for $C_{15}H_{16}O_3$ (FW 244.23): C, 73.77; H, 6.14 %. Found: C, 73.62; H, 6.28 %. IR (KBr, cm^{-1}): 3378 (OH), 1625 (C=O), 1456 (C=C). ^{1}H-NMR ($CDCl_3$, δ / ppm): 0.90 (6H, *s*, 2×CH_3), 2.43 (4H, *s*, 2×CH_2), 4.60 (1H, *s*, OH), 6.40–7.24 (5H, *m*, ArH and C–H). ^{13}C-NMR: 28.76 (2×CH_3), 32.16 (2×CH_2), 112.45, 131.53–141.47 (C=C and ArC), 162.52 (2×C=O).

*3-(4-Methoxyphenyl)-6,6-dimethyl-3,3a,6,7-tetrahydro-5*H*-2,1-benzisoxazol-4-one (**5a**)*. Yield: 71 %; m.p. 110 °C. Anal. Calcd. for $C_{16}H_{19}NO_3$ (FW 273.38): C, 70.32; H, 6.95; N, 5.12 %. Found: C, 70.09; H, 6.74; N, 5.22 %. IR (KBr, cm^{-1}): 1670 (C=O), 1562 (C=N),1230 (–C–O–N–). ^{1}H-NMR ($CDCl_3$, δ / ppm): 1.01 (6H, *s*, 2×CH_3), 2.09 (2H, *s*, CH_2), 2.46 (2H, *s*, CH_2), 3.63 (1H, *d*, *J* = 7.5 Hz, CH), 3.92 (3H, *s*, OCH_3), 4.58 (1H, *d*, *J* = 6.2 Hz, CH), 6.85–7.89 (4H, *dd*, *J* = = 7.2 Hz, ArH). ^{13}C-NMR: 27.32 (2×CH_3), 29.32 (CH_2), 31.38 (CH_2), 40.23 (OCH_3), 62.21 (CH), 72.34 (CH), 128–142.64 (ArC), 154.25 (C=N), 168.25 (C=O). MS (*m*/*z*): 273 (M^+).

*3-(4-Chlorophenyl)-6,6-dimethyl-3,3a,6,7-tetrahydro-5*H*-benzisoxazol-4-one (**5b**)*. Yield: 69 %; m.p. 100 °C. Anal. Calcd. for $C_{15}H_{16}NO_2Cl$ (FW 277.67): C, 64.86; H, 5.76; N, 5.04 %. Found: C, 64.99; H, 5.62; N, 5.12 %. IR (KBr, cm^{-1}): 1670 (C=O), 1534 (C=N), 1226 (–C–O–N–), 627 (C–Cl). ^{1}H-NMR ($CDCl_3$, δ / ppm): 1.014 (6H, *s*, 2×CH_3), 2.09 (2H, *s*, CH_2), 2.46 (2H, *s*, CH_2), 3.64 (1H, *d*, *J* = 7.1 Hz, C–H), 4.32 (1H, *d*, *J* = 6.4 Hz, C–H), 6.65–7.72 (4H, *dd*, *J*= 7.1 Hz, ArH). ^{13}C-NMR: 27.68 (2×CH_3), 29.87 (CH_2), 31.65 (CH_2), 61.78 (CH), 72.88 (CH), 129.5–143.25 (ArC), 154.53 (C=N), 164.56 (C=O). MS (*m*/*z*): 278 (M^+).

*3-(4-Hydroxyphenyl)-6,6-dimethyl-3,3a,6,7-tetrahydro-5*H*-benzisoxazol-4--one (**5c**)*. Yield: 72 %; m.p. 102 °C. Anal. Calcd. for $C_{15}H_{17}NO_3$ (FW 259.23): C, 69.49; H, 6.53; N, 5.40 %. Found: C, 69.22; H, 6.62; N, 5.56 %. IR (KBr, cm^{-1}): 3378 (OH), 1670 (C=O), 1574 (C=N), 1223 (–C–O–N–). ^{1}H-NMR ($CDCl_3$, δ / / ppm): 0.97 (6H, *s*, 2×CH_3), 2.18 (2H, *s*, CH_2), 2.43 (2H, *s*, CH_2), 3.72 (1H, *d*, *J* = 7.2 Hz, C–H), 4.43 (1H, *d*, *J* = 6.3 Hz, C–H), 4.75 (1H, *s*, OH), 6.62–7.24

(4H, *dd*, *J* = 7.2 Hz, ArH). ^{13}C-NMR: 28.76 (2×CH_3), 29.55 (CH_2), 32.16 (CH_2), 62.34 (CH), 71.67 (CH), 131.53–141.47 (ArC), 153.51 (C=N), 162.52 (C=O).

*3-(4-Methoxyphenyl)-6,6-dimethyl-2-phenyl-2,3,3a,5,6,7-hexahydro-4*H-*indazol-4-one (**6a**)*. Yield: 70 %; m.p. 172 °C. Anal. Calcd. for $C_{22}H_{24}N_2O_2$ (FW 364.42): C, 72.52; H, 6.59; N, 7.69 %. Found: C, 72.12; H, 6.08; N, 7.34%. IR (KBr, cm^{-1}): 1670 (C=O), 1585 (C=N), 1490 (N–N). ^{1}H-NMR ($CDCl_3$, δ / ppm): 0.96 (6H, *s*, 2×CH_3), 2.19 (2H, *s*, CH_2), 2.46 (2H, *s*, CH_2), 3.64 (1H, *d*, *J* = 7.3 Hz, CH), 4.43 (1H, *d*, *J* = 6.2 Hz, CH), 6.86–8.00 (9H, *m*, ArH); ^{13}C-NMR: 27.32 (2×CH_3), 29.55 (CH_2), 31.38 (CH_2), 40.23 (OCH_3), 63.21 (CH), 71.23 (CH), 128–139.64 (ArC), 152.35 (C=N), 168.25 (C=O). MS (*m*/*z*): 348 (M^+).

3-(4-Chlorophenyl)-6,6-dimethyl-2-phenyl-2,3,3a,5,6,7-hexahydro-H-*indazol-4-one (**6b**)*. Yield: 79 %; m.p. 152 °C. Anal. Calcd. for $C_{21}H_{21}N_2OCl$ (FW 352.77): C, 71.38; H, 5.94; N, 7.93 %. Found: C, 71.02; H, 6.23; N, 7.45 %. IR (KBr, cm^{-1}): 1670 (C=O), 1562 (C=N), 1454 (N–N), 627 (C–Cl). ^{1}H-NMR ($CDCl_3$, δ / ppm): 0.96 (6H, *s*, 2×CH_3), 2.19 (2H, *s*, CH_2), 2.46 (2H, *s*, CH_2), 3.72 (1H, *d*, *J* = 7 Hz, C–H), 4.43 (1H, *d*, *J* = 6.3 Hz, C–H), 6.86–8.00 (9H, *m*, ArH). ^{13}C-NMR: 27.68 (2×CH_3), 29.23 (CH_2), 31.65 (CH_2), 61.45 (CH), 70.23 (CH), 129.5–139.25 (ArC), 155.35 (C=N), 164.56 (C=O). MS (*m*/*z*): 353 (M^+).

3-(4-Hydroxyphenyl)-6,6-dimethyl-2-phenyl-2,3,3a,5,6,7-hexahydro-H-*indazol-4-one (**6c**)*. Yield: 74 %; m.p. 158 °C. Anal. Calcd. for $C_{21}H_{22}N_2O_2$ (FW 334.43): C, 75.44; H, 6.58; N, 8.38 %. Found: C, 74.87; H, 6.24; N, 8.12 %. IR (KBr, cm^{-1}): 3378 (OH), 1670 (C=O), 1538 (C=N), 1486 (N–N). ^{1}H-NMR ($CDCl_3$, δ / ppm): 0.91 (6H, *s*, 2×CH_3), 2.12 (2H, *s*, CH_2), 2.39 (2H, *s*, CH_2), 3.45 (1H, *d*, *J* = 7.1 Hz, C–H), 4.21 (1H, *d*, *J* = 6.1 Hz, C–H), 4.58 (1H, *s*, OH), 6.52–7.193 (9H, *m*, ArH). ^{13}C-NMR: 28.76 (2×CH_3), 29.21 (CH_2), 32.16 (CH_2), 63.21 (CH), 72.87 (CH), 128.53–138.47 (ArC), 154.48 (C=N), 162.52 (C=O).

*3-[(4-Chlorobenzylidene)amino]-5-(4-hydroxybenzylidene)-2-thioxoimidazolidin-4-one (**4a**)*. Yield: 72 %; m.p. 304 °C. Anal. Calcd. for $C_{17}H_{12}N_3O_2SCl$ (FW 357.72): C, 57.00; H, 3.35; N, 11.75; S, 8.95 %. Found: C, 56.55; H, 3.62; N, 11.35; S, 8.85 %. IR (KBr, cm^{-1}): 3480 (OH), 3348 (NH), 1705 (C=N), 1311 (C=S), 610 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 4.62 (1H, *s*, OH), 6.90–7.21 (9H, *m*, ArH and C–H), 8.25 (1H, *s*, CH=N), 10.21 (1H, *s*, NH). ^{13}C-NMR: 129.34–135.34 (ArC and C–H), 155.09 (C=N), 163.24 (C=O), 178.23 (C=S). MS (*m*/*z*): 358 (M^+).

*3-[(4-Chlorobenzylidene)amino]-5-(4-hydrozbenzylidene)-2-thioxoimidazolidin-4-one (**4b**)*. Yield: 79 %; m.p. 320 °C. Anal. Calcd. for $C_{19}H_{17}N_4OSCl$ (FW 384.78): C, 59.29; H, 4.42; N, 14.56; S, 8.32 %. Found: C, 59.32; H, 4.52; N, 14.22; S, 8.48 %. IR (KBr, cm^{-1}): 3322 (NH), 1735 (C=N), 1348 (C=S), 628 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 2.95 (6H, *s*, $N(CH_3)_2$), 7.12–7.77 (9H, *m*, ArH and C–H), 8.45 (1H, *s*, CH=N), 11.80 (1H, *s*, NH). ^{13}C-NMR: 32.34 ($N(CH_3)_2$),

128–135.48 (ArC and C–H), 155.55 (C=N), 166.28 (C=O), 178.87 (C=S). MS (*m*/*z*): 385 (M^+).

*3-[(4-Chlorobenzylidene)amino]-5-(4-methoxybenzylidene)-2-thioxoimidazolidin-4-one (**4c**)*. Yield: 74 %; m.p. 300 °C. Anal. Calcd. for $C_{18}H_{14}N_3O_2SCl$ (FW 371.74): C, 58.14; H, 3.76; N, 11.3; S, 8.60 %. Found: C, 58.24; H, 3.52; N, 11.52; S, 8.52 %. IR (KBr, cm^{-1}): 3295 (NH), 1680 (C=N), 1286 (C=S), 638 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 3.98 (3H, *s*, OCH_3), 6.79–7.58 (9H, *m*, ArH and C–H), 8.25 (1H, *s*, CH=N), 9.84 (1H, *s*, NH). ^{13}C-NMR: 34.43 (OCH_3), 128––135.5 (ArC and C–H), 156.25 (C=N), 163.24 (C=O), 179.34 (C=S).

*6-[(4-Chlorobenzylidene)amino]-3-(4-hydroxyphenyl)-3a,4-dihydro-3*H,*6*H-*-imidazo[4,5-*c*]isoxazole-5-thione (**7a**)*. Yield: 56 %; m.p. 258 °C. Anal. Calcd. for $C_{17}H_{13}N_4O_2SCl$ (FW 372.73): C, 54.76; H, 3.42; N, 15.03; S, 8.52 %. Found: C, 54.35; H, 3.52; N, 14.85; S, 8.38 %. IR (KBr, cm^{-1}): 3442 (OH), 3337 (NH), 1715 (C=N), 1220 (–C–O–N–), 1341 (C=S), 620 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 3.70 (1H, *d*, *J* = 6.3 Hz, CH), 4.23 (1H, *d*, *J* = 6.8 Hz, C_4–H of isoxazole), 4.34 (1H, *s*, OH), 6.90–7.75 (8H, *m*, ArH), 8.25 (1H, *s*, CH=N), 10.13 (1H, *s*, NH). ^{13}C-NMR: 62.23 (CH), 72.23 (CH), 129–136 (ArC), 155.09 and 158.23 (2×C=N), 179.43 (C=S). MS (*m*/*z*): 373 (M^+).

*6-[(4-Chlorobenzylidene)amino]-3-[4-(dimethylamino)phenyl]-3a,4-dihydro-3*H,*6*H-*imidazo[4,5-*c*]isoxazole-5-thione (**7b**)*. Yield: 59 %; m.p. 275 °C. Anal. Calcd. for $C_{19}H_{18}N_5OSCl$ (FW 399.79): C, 59.45; H, 4.69; N, 18.25; S, 8.34 %. Found: C, 59.32; H, 4.74; N, 18.42, S, 8.38 %. IR (KBr, cm^{-1}): 3242 (NH), 1675 (C=N), 1321 (C=S), 1240 (–C–O–N–), 620 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 2.90 (6H, *s*, $N(CH_3)_2$), 3.92 (1H, *d*, *J* = 6.0 Hz, CH), 4.32 (1H, *d*, *J* = 6.6 Hz, C_4–H of isoxazole), 6.91–7.98 (8H, *m*, ArH), 8.22 (1H, *s*, CH=N), 11.92 (1H, s, NH). ^{13}C-NMR: 30.23 ($N(CH_3)_2$), 61.23 (CH), 71.45 (CH), 129–136 (ArC), 155.09 and 157.65 (2×C=N), 181.11 (C=S). MS (*m*/*z*): 400 (M^+).

*6-[4-Chlorobezylidene)amino]-3-(4-methoxyphenyl)-3a,4-dihydro-3*H,*6*H-*-imidazo[4,5-*c*]isoxazole-5-thione (**7c**)*. Yield: 62 %; m.p. 276 °C. Anal. Calcd. for $C_{18}H_{15}N_4O_2SCl$ (FW 386.44): C, 55.74; H, 3.88; N, 14.48; S, 8.27 %. Found: C, 55.83; H, 3.68; N, 14.52; S, 8.63 %. IR (KBr, cm^{-1}): 3322 (NH), 1662 (C=N), 1342 (C=S), 1263 (–C–O–N–), 626 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 3.73 (1H, *d*, *J* = 6.3 Hz, CH), 3.96 (3H, *s*, OCH_3), 4.32 (1H, *d*, *J* = 7.0 Hz, C_4–H of isoxazole), 6.79–7.58 (8H, *m*, ArH), 8.00 (1H, *s*, CH=N), 10.22 (1H, *s*, NH). ^{13}C-NMR: 31.54 (OCH_3), 63.43 (CH), 72.45 (CH), 127.67–135.56 (ArC), 153.21 and 156.08 (2×C=N), 184.76 (C=S).

*6-[(4-Chlorobenzylidene)amino]-3-(4-hydroxyphenyl)-2-phenyl-2,3,3a,4-tetrahydro-6*H-*imidazo[4,5-*c*]-pyrazole-5-thione (**8a**)*. Yield: 64 %; m.p. 156 °C. Anal. Calcd. for $C_{23}H_{18}N_5OSCl$ (FW 447.68): C, 61.60; H, 4.02; N, 15.62; S, 7.14 %. Found: C, 61.25; H, 4.21; N, 15.24; S, 6.89 %. IR (KBr, cm^{-1}): 3456

(OH), 3127 (NH), 1584 (C=N), 1442 (N–N), 1344 (C=S) 624 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 3.59 (1H, *d*, *J* = 6.3 Hz, CH), 4.34 (1H, *d*, *J* = 7.0 Hz, C_4–H of pyrazole), 5.75 (1H, *s*, OH), 6.90–7.42 (13H, *m*, ArH), 8.35 (1H, *s*, CH=N), 10.3 (1H, *s*, NH). ^{13}C-NMR: 63.23 (CH), 72.54 (CH), 128.23–136.43 (ArC), 155.09 and 153.12 (2×C=N), 182.54 (C=S). MS (*m*/*z*): 448 (M^+).

*6-[(4-Chlorobenyzlidene)amino]-3-p4-dimethylamino)phenyl]-2-phenyl--2,3,3a,4-tetrahydro-6*H-*imidazo[4,5-*c]*pyrazole-5-thione (**8b**)*. Yield: 64 %; m.p. 142 °C. Anal. Calcd. for $C_{25}H_{23}N_6SCl$ (FW 474.92: C, 63.22; H, 4.84; N, 17.70; S, 6.74 %. Found: C, 63.11; H, 4.64; N, 17.54; S, 6.34 %. IR (KBr, cm^{-1}): 3124 (NH), 1564 (C=N), 1452 (N=N), 1422 (N–N),1324 (C=S), 638 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 2.84 (6H, *s*, $N(CH_3)_2$), 3.54 (1H, *d*, *J* = 6.2 Hz, CH), 4.34 (1H, *d*, *J* = 7.3 Hz, C_4–H of pyrazole), 6.90–7.42 (13H, *m*, ArH), 8.25 (1H, *s*, CH=N), 10.42 (1H, *s*, NH). ^{13}C-NMR: 31.23 ($N(CH_3)_2$), 62.43 (CH), 73.34 (CH), 128.32–135.65 (ArC), 152.45 and 156.11 (2×C=N), 180.23 (C=S). MS (*m*/*z*): 475 (M^+).

*6-[(4-Chlorobenzylidene)amino]-3-(4-methoxyphenyl)-2-phenyl-2,3,3a,4-tetrahydro-6*H-*imidazo[4,5-*c*]-pyrazole-5-thione (**8c**)*. Yield: 68 %; m.p. 164 °C. Anal. Calcd. for $C_{24}H_{20}N_5OSCl$ (FW 451.86): C, 66.4; H, 4.33; N, 15.16; S, 6.93 %. Found: C, 66.24; H, 4.53; N, 15.23; S, 6.63 %; IR (KBr, cm^{-1}): 3193 (NH), 1538 (C=N), 1444 (N=N), 1417 (N–N), 1351 (C=S), 623 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 3.76 (1H, *d*, *J* = 6.8 Hz, CH), 3.90 (3H, *s*, OCH_3), 4.43 (1H, *d*, *J* = 7.3 Hz, C_4–H of pyrazole), 6.8–7.7 (13H, *m*, ArH), 8.23 (1H, *s*, CH=N), 10.72 (1H, *s*, NH). ^{13}C-NMR: 34.23 (OCH_3), 63.23 (CH), 72.56 (CH), 129–136 (ArC), 152.21 and 155.23 (2×C=N), 179.57 (C=S).

Antibacterial activity

The newly synthesized compounds (**5**–**8**) were screened for their antibacterial activity against *Escherichia coli* (ATCC-25922), *Staphyllococcus aureus* (ATCC-27853), *Corynebacterium diphtheriae* and *Proteus aeruginosa* (recultured) bacterial strains by the disc diffusion method.[19] The activity of the tested compounds and that of the standard drug, ampicillin, are reported in Table I together with their estimated partition coefficients (log *P*).[20]

EXPERIMENTAL

Chemistry

All chemicals were supplied by E. Merck (Germany) and S. D. Fine Chemicals (India). The melting points of the synthesized compounds were determined in open capillary tubes using a Veego VMP-1 melting point apparatus and are expressed in °C and uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as the visualizing agent. The IR spectra in KBr pellets were recorded on a Perkin–Elmer spectrophotometer in the range of 4000–400 cm^{-1}. The ^{1}H-NMR spectra were recorded on a Brucker Avance 500 MHz NMR spectrometer from International Equipment Trading Ltd., using $CDCl_3$ or DMSO-d_6 as the solvent and

TABLE I. Antibacterial activity of compounds **5**–**8**

Compound	Zone of inhibition / mm				log *P*
	Gram-positive		Gram-negative		
	S. aureus	*C. diphtheriae*	*E. coli*	*P. aeruginosa*	
5a	16	10	8	8	3.20
5b	13	12	9	9	3.96
5c	12	11	10	10	3.06
6a	21	10	9	9	4.77
6b	17	12	10	10	5.53
6c	12	18	9	9	4.62
7a	10	14	8	8	4.09
7b	21	17	11	11	4.50
7c	14	20	10	10	4.28
8a	13	16	9	9	5.66
8b	20	18	9	9	6.07
8c	16	15	10	10	5.81
DMSO	–	–	–	–	–
Ampicillin	26	23	32	32	–

TMS as the internal standard. The mass spectra were taken on a Jeol SX-102/PA-6000 (EI) spectrometer. C,H,N estimation was realized on a Carlo Erba 1108 (CHN) elemental analyser.

*Preparation of 2-arylidene-5,5-dimethylcyclohexane-1,3-dione (**3a**–**c**)*

A mixture of 5,5-dimethylcyclohexane-1,3-dione **(1)** (1.41 mg, 0.010 mol), a substituted aromatic aldehyde (0.010 mol) and KOH (0.0050 mol) in ethanol (8.0 mL) was refluxed for 3 h. After monitoring the reaction by TLC, the reaction mixture was cooled to room temperature, poured onto ice, filtered and recrystallized from ethanol.

*General procedure for the synthesis of 5-arylidene-3-[(4-chlorobenzylidene)amino]-2-thioxoimidazolidin-4-one (**4a**–**c**)*

A mixture of 3-[(4-chlorobenzylidene)amino]-2-thioxoimidazolidin-4-one (**2**) (0.010 mol), an aromatic aldehyde (0.010 mol) and piperidine (0.0050 mol) was fused at 120–130 °C for 2 h. The reaction mixture was cooled and acidified with 2 M hydrochloride acid. The crude product was filtered off, washed with water, dried and purified by recrystallization from acetic acid.

*General procedure for the synthesis of 6,6-dimethyl-3-(substituted phenyl)-3,3a,6,7-tetrahydro--5*H*-2,1-benzisoxazol-4-one (**5a**–**c**)*

An equimolar mixture of **3** (0.010 mol) and hydroxylamine hydrochloride (0.010 mol) in (8.0 mL) glacial acetic acid was refluxed for 8 h after which the reaction mixture was concentrated and cooled. The formed crystals were filtered, washed with petroleum ether and recrystallized from ethanol.

*General procedure for the synthesis of 3-(substituted phenyl)-6,6-dimethyl-2-phenyl--2,3,3a,5,6,7-hexahydro-4*H*-indazol-4-one (**6a**–**c**)*

A mixture of compound **3** (0.010 mol), phenylhydrazine (0.010 mol) and KOH (0.010 mol) in (8.0 mL) ethanol was refluxed for 3 h. The concentrated reaction mixture was poured onto ice and acidified with 2 M HCl. The resultant solid was filtered, dried and recrystallized from ethanol.

*General procedure for the synthesis of 6-{[(4-chlorobenzylidene]amino]-3-(substituted phenyl)-3a,4-dihydro-3*H,*6*H-*imidazo[4,5-*c*]isoxazole-5-thione (**7a–c**)*

A mixture of compound **4** (0.010 mol) and hydroxylamine hydrochloride (0.030 mol) in (8.0 mL) glacial acetic acid was refluxed for 9 h after which the reaction mixture was concentrated and cooled. The formed crystals were filtered, washed with petroleum ether and ethyl acetate.

*General procedure for the synthesis of 6-[(4-chlorobenzylidene)amino-2-phenyl-3-substitutedphenyl)2,3,3a,4-tetrahydro-6*H-*imidazo[4,5-*c*]pyrazole-5-thione (**8a–c**)*

A mixture of compound **4** (0.010 mol), phenylhydrazine (0.030 mol) and KOH (0.0050 mol) in (8.0 mL) ethanol was refluxed for 5 h. The concentrated reaction mixture was poured onto ice and acidified with 2 M HCl. The resultant solid was filtered, dried and recrystallized from glacial acidic acid.

Antibacterial testing

The newly synthesized compounds (**5**(**a**–**c**)–**8**(**a**–**c**)) were screened for their antibacterial activity against *Escherichia coli* (ATCC-25922), *Staphyllococcus aureus* (ATCC-27853), *Corynebacterium diphtheriae* and *Proteus aeruginosa* (recultured) bacterial strains by the disc diffusion method.[19] The discs (6 mm) were prepared from Whatman filter paper and used after autoclaving at 121 psi for 15 min and drying in a hot air oven. Bacterial inocula equivalent to the 0.5 McFarland turbidity standard were prepared in normal saline and subsequently diluted. The compounds were dissolved in DMSO and tested at a concentration of 250 μg/ml. The zone of inhibition after 16–18 h incubation was measured in mm and the potency was compared with the standard drug ampicillin trihydrate.

CONCLUSIONS

A number of isoxazole and pyrazole derivatives (**5**–**8**) were prepared and evaluated for their *in vitro* antibacterial activity.[19] The partition coefficients[20] of the compounds were estimated. All the tested compounds were found to be ideal drug candidates, except for a few which had log *P* value above the requirement, which specifies that an ideal drug candidate should have a log *P* value in the range –0.5 to +5.0,[21] or should be less than 4.5 as calculated by Moriguchi method.[22] Although the compound **6a**, **7b**, **8b** and **8c** showed good inhibition activity towards Gram-positive bacteria, *i.e. S. aureus* and *C. diphtheriae*, their inhibition potency was not in linear correlation with their log *P* values. Thus, it may be concluded that besides lipophilicity, electronic and steric effects may be influencing the activity. The compounds **8a**–**c**, having high log *P* values, may cause absorption and distribution problems. Hence, for further development, compounds having lower estimated log *P* values should be prepared.

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ИЗВОД

СИНТЕЗА И КАРАКТЕРИЗАЦИЈА ОДАБРАНИХ КОНДЕНЗОВАНИХ ИЗОКСАЗОЛСКИХ И ПИРАЗОЛСКИХ ДЕРИВАТА И ЊИХОВА АНТИМИКРОБНА АКТИВНОСТ

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Нови потентни антибактерициди, кондензовани изоксазолски и пиразолски деривати, добијени су из 5,5-диметилциклохексан-1,3-диона (**1**) и 3-[(4-хлоробензилиден)амино]-2-тиоксоимидазолидин-4-она (**2**) као синтона. Кондензацијом ароматичних алдехида са **1** или **2** граде се 2-арилиден-5,5-диметилциклохексан-1,3-дион (**3**), односно 5-арилиден-3-[(4-хлоробензилиден)амино]-2-тиоксоимидазолидин-4-он (**4**). Хетероциклизацијом једињења **3** и **4** у присуству нуклеофилних реагенаса добијају се поменута једињења (**5**–**8**). Новосинтетисани хетероцикли су окарактерисани на основу хемијских особина и спектроскопских података. Једињења **5**–**8** инхибирају *S. aureus* и *C. diphtheriae.*

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